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Vol. 211, No. 4 APRIL, 1946 No. 889

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

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THE AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

APRIL, 1946

ORIGINAL ARTICLES

THE COURSE OF FILARIASIS AFTER REMOVAL FROM AN ENDEMIC AREA

By Captain Alton W. Behm, M.C., A.U.S.
and
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During the past 2½ years a number of reports on the early manifestations of filariasis have appeared.[3] These in general have been based on the results of the examination of troops in endemic areas or of those evacuated because of the diagnosis of this disease. They have provided new and important information on the incubation period and initial symptoms of infection with *W. bancrofti* in young adult while males.

It will, of course, be a number of years before final appraisal can be made of the results of exposure of troops in endemic areas. It seems worth while, however, to present an "interim report" on the history and condition of 532 men 2 years after leaving the island Tonga-tabu, a highly endemic area, where they had been on duty from May 1942 to May 1943. A report of the symptoms which developed in these men in the latter part of 1943 has already been published.[5]

In addition to these men, who will be referred to as Group A, 2 groups of replacements had been evacuated with them. The larger of these, consisting of 145 men (Group B) had joined the units after Group A had left Tonga-tabu, but were stationed with them for 6 months in 1943 on Woodlark Island, one of the Trobriands, which lie off the eastern end of New Guinea. While this island is in the filarial zone, and the disease presumably exists among the natives, as far as can be ascertained from medical officers who were stationed there it is at least uncommon and no record of a native infected with filaria has been uncovered. Yet, as will be shown, the men in Group B developed the same symptoms as those in Group A, and *at the same time*. Group C comprised 32 men who were late replacements and had never been in an endemic area.

While complete medical histories have not been available, the notes of the Battalion Surgeon for the larger element of the groups after they had reached Woodlark Island, and the results of a survey for filariasis made at a general hospital overseas in January 1944 have been most helpful.[1a] The 532 men forming the basis of this report do not constitute the total number exposed on Tonga-tabu. Some had been evacuated from Woodlark or Australia with the clinical diagnosis of filariasis, or for other reasons, before coming under our observation.

Since microfilariæ in the peripheral blood or adult worms in biopsy material have been demonstrated in only a very small number of these cases, it has been

necessary in the majority to make the diagnosis solely on clinical grounds. In the absence of repeated observed attacks of lymphadenitis, retrograde lymphangitis, or scrotal swelling for which no other cause can be found, in an individual known to have been in an endemic area, the diagnosis of filariasis is difficult and often must be uncertain. Emphasis is placed on observed physical findings, because men who have seen elephantiasis among natives, and who have been subjected to repeated questioning and examination, very naturally have developed pronounced anxiety concerning the effect possible infection in them may have. They have tended to exaggerate symptoms and to worry about every minor twinge or discomfort in arms, legs or scrotum, no matter what the cause. Rome and Fogel[9] called attention to this understandable emotional overlay, to which the admitted lack of knowledge by medical officers at the time of the course and possible sequelæ of this disease contributed. Factual knowledge was necessary for the proper handling of these men. Augustine[1] has recently stated his belief that "the evidence at hand is insufficient to warrant making a diagnosis of bancroftian filariasis on all cases from the South Pacific in which lymphadenitis, lymphangitis or suggestive genital signs may have occurred."

The early symptoms of filariasis as observed in troops have consisted of attacks of lymphangitis, lymphadenitis, funiculitis, epididymitis and swelling of the testicles. These attacks usually last from 3 to 5 days, occasionally 10 days to 2 weeks, and rarely as long as a month. In a fair proportion of cases the attack is preceded by malaise, and accompanied by fever, usually low, but occasionally as high as 103° to 104° F. With the subsidence of the attack, the pain disappears and the swelling diminishes, although palpable enlargement of lymph nodes or palpably thickened lymphatics may persist. The lymphangitis is the most striking and characteristic feature of these attacks. In contrast to the usual lymphangitis of bacterial infection, it is retrograde, proceeding in the course of 1 to 3 days from the axilla down the arm toward the elbow, or from the epitrochlear or anticubital region down the forearm to the wrist and hand. This lymphangitis is manifest by red linear streaks, palpable lymphatic vessels, and edema without local heat. In the lower extremity it progresses from the inguinal region down the inner aspect of the thigh or, quite characteristically, around the lateral aspect of the thigh, above the greater trochanter, to the gluteal region.

On admission of these men to the hospital, in addition to a routine medical history, special questions concerning itinerary, living conditions, contact with natives, type of duty, symptoms of possible filariasis, with dates and recurrences, were asked and recorded on work sheets. During the physical examination special attention was paid to palpable lymph nodes, lymphangitis, and abnormalities of the scrotum and its contents. In addition to the routine blood count, Kahn test, urine and stool examination, the blood of each man was examined repeatedly for microfilaria, both day and night, in thick smears and by Knott's method, using 1 to 20 cc. of blood. Intradermal tests with an extract of *Dirofilaria immitis* were carried out according to the technique of Bozicevich and Hutton.

Only 83 men (15%) of Group A denied all symptoms suggestive of filariasis. One-quarter of the group (133) believed that they were physically able to do full duty, while 24 (4.5%) felt themselves incapacitated by the disease for any type of duty. The remaining 373 (70.5%) believed that they could do only some type of limited duty. There were 252 (47.3%) who claimed that exercise produced symptoms, 77 that hot weather made them worse. Thirty-three believed their sexual potency to have been impaired. The opinion of the men in the other groups was not very different; 52.4% of Group B believed themselves fit only for light duty, and only 44.8% did not complain of symptoms sug-

gestive of filariasis. It is noteworthy that in the small Group C composed of men who had never been exposed, 8 men (25%) believed that they could only do light duty, while 2 believed that they were totally incapacitated for any type of duty by filariasis. These facts bring out the importance of psychologic factors and anxiety in men among whom a new and little understood disease appears.

During the period of exposure the men had lived in unscreened tents, but were provided with mosquito nets for sleeping. Contact with natives is said to have been common. The filariasis on Tonga-tabu is of the non-periodic type, that is, among natives microfilariæ can be found in the peripheral blood during both day and night. The common vector is said to be *Aëdes scutellaris*. There was no difference in the incidence of symptoms among men whose duties had been in the jungle, on patrol, etc., and cooks, clerks and others, whose duties had been chiefly around camps.

According to the histories given by Group A, the first symptoms suggestive of filariasis developed between 2 and 3 months after the first exposure, the incidence remaining low, however, during the first year, and increasing sharply some 14 months after first possible exposure while they were stationed on Woodlark. None of the symptoms occurring during the year on Tonga-tabu were recognized at the time as due to filariasis. The time of initial symptoms is shown in Figure 1. This "incubation" period is similar to that reported by King[3] and others. It is not an accurate picture of the group, however, since it does not include the men, something in excess of 60, who had been evacuated separately and were not available for study. Also shown in Figure 1 is the time of onset of symptoms of 62 men in Group B in whom this could be dated. If this was filariasis in Group B, symptoms began to develop in less than 2 months after first possible exposure, and reached a maximum incidence in 5 months instead of 17 to 18 months as in Group A.

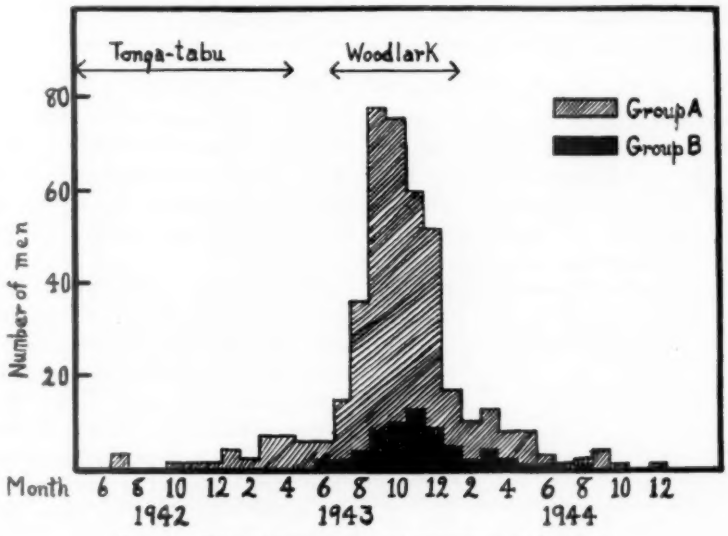

FIG. 1.—Date of first symptoms suggestive of filariasis.

The site of the initial attack in Group A, as obtained from the histories, is shown in Table 1. Subsequent attacks involved the same area as the original or another region. That is, 1 man would give a history of repeated swelling of the epitrochlear nodes in one arm, while in another the initial

involvement might be in the scrotum, and the 2d attack involve the lymphatic structures of the arm. A summary of the areas involved in all attacks is shown in Table 2.

TABLE 1.—SITE OF INITIAL SYMPTOMS IN GROUP A

Scrotal swelling	105
Axillary adenitis	28
Epitrochlear adenitis	30
Inguinal adenitis	63
Cervical adenitis	9
Multiple sites	121

TABLE 2.—INCIDENCE OF INVOLVEMENT IN REPEATED ATTACKS IN GROUP A

Scrotal swelling	262
Axillary and epitrochlear	187
Inguinal and femoral	161
Cervical	21

A history of the number of attacks experienced was difficult to obtain. Some men gave excellent accounts of clear-cut attacks. Others claimed that they had never been free from symptoms since onset. The majority of these, however, showed no demonstrable physical abnormality. Omitting such cases, the number of attacks varied from 1 to 12. The distribution is shown in Table 3.

TABLE 3.—NUMBER OF ATTACKS OF LYMPHANGITIS, ADENITIS, OR GENITAL INVOLVEMENT

No. attacks	Men
1	139
2	99
3	76
4	53
5	21
6	10
7	1
8	2
10	3
12	3
13	1

The results of physical examination in September 1944 are shown in Table 4. Any palpable epitrochlear or axillary lymph nodes have been recorded. Small, discrete, non-tender inguinal glands, which would be graded 1 plus on a scale in which a gland 1 cm. in diameter would be called 4 plus, have not been recorded.

No microfilariæ were found in the peripheral blood of any of these groups while at the hospital. Microfilariæ had been repeatedly demonstrated, however, in one man of Group A while on Woodlark, and in a second before arrival at this hospital. Neither of these men were available for study. In addition to these 2, the records of 2 other men of Group A recorded the finding of a single microfilaria on one examination. These two were examined repeatedly over a period of several months, but no microfilariæ could be found.

TABLE 4.—POSITIVE FINDINGS ON PHYSICAL EXAMINATION IN GROUP A

Axillary adenitis	167
Epitrochlear adenitis	62
Inguinal adenitis	272
Femoral adenitis	167
Enlarged epididymis or testicle	34
Thickened cord	63
Chronic lymphangitis	5

Biopsies of lymph nodes had been performed on 13 men before they came under observation at this hospital. Adult worms were found in sections from 2 cases. We performed biopsies in 7 other cases; in 1 a microfilaria was found in a thrombosed lymphatic.

These entire groups were kept under observation for from 2 to 10 months. During this period a number developed attacks of lymphadenitis, lymphangitis, or scrotal swelling, believed due to filariasis. Some attacks developed spontaneously, the majority were precipitated by exercise. The incidence and severity of attacks diminished with the time since leaving the endemic area. The relation of the time of last attack and removal from the endemic area is shown in Figure 2. All patients were subjected to a month's intensive training without symptoms before being regarded as free from attacks. Many men complained of pains in arms or legs, unaccompanied by swelling, after exercise. Since the pathology of early filariasis is either the result of lymphatic obstruction or an allergic reaction to the liberation of antigen from adult worms, it is believed that a complaint of pain without swelling is more properly interpreted as due to muscle strain, fatigue, arthritis, neuritis or some other cause rather than filariasis.

In Group A, a "definite" clinical diagnosis of infection had been made in 104

men in the fall of 1943 while they were still on Woodlark Island and a "possible" diagnosis in an additional 68. A "definite" clinical diagnosis had also been made in 10 men in Group B, and a "probable" diagnosis in an additional 4. The conclusions of the survey made by a General Hospital overseas in January 1944 was that 67.8% of Group A were presumably infected, and that there were suggestive symptoms in another 24.7%, leaving only 7.5% believed to be free from suspicion of infection. In Group B, 21.1% were believed to be infected, and infection probable in an additional 29.4%.

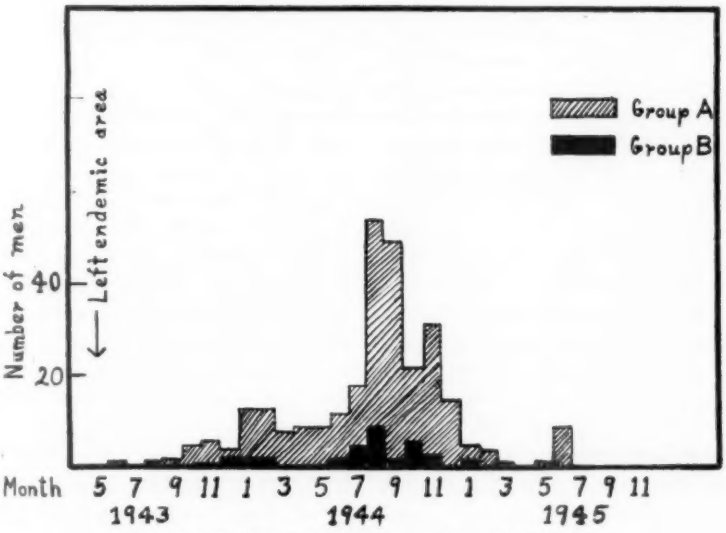

FIG. 2.—Date of last attack suggestive of filariasis.

It would, of course, be extremely helpful to have some reliable laboratory test which would either exclude filarial infection, or if the error consisted of false negative reactions, could be trusted to establish it. The most promising of such tests is the skin test. Unfortunately, antigens prepared from *W. bancrofti* are not available. Those that have been used are prepared from other filarial worms, most work having been done with extracts of the dog heart worm, *D. immitis*. This test was developed independently by Taliaferro and Hoffman[11] and by Fairley.[4] In an effort to eliminate false positive reactions Bozicevich and Hutter[2] used a 1:8000 extract instead of the 1:1000 used by Taliaferro and Fairley and in addition used a control of the same dilution of dog serum protein.

Bozicevich and Hutter reported no false positives in men who had never been in an endemic area. Using their technique 2 of 32 men, or 6% in Group C gave positive reaction. King, using a 1:1000 antigen prepared according to Fairley's technique, got 10.5% positive reactions in 171 controls. Using the same antigen, the overseas General Hospital referred to above obtained 11% positive reactions in 100 men recently arrived from the United States, and 18% in 72 men without symptoms but who had had some service in New Guinea in an area in which filariasis has not been recognized among troops. The results of skin tests in Groups A, B and C are given in Table 5.

TABLE 5.—PERCENTAGE POSITIVE SKIN TESTS WITH D. IMMITIS ANTIGEN

	Feb.-March 1944 1:1000	Sept. 1944 1:8000
Group A	73.9	57.7
Group B	27.9	18.3
Group C	..	6.0

These results pose some problems in interpretation. The positive reactions in Group C may be accepted as "false positive," and is the same order of frequency as that obtained by King although higher than by Bozicevich and Hutter. The slightly higher incidence (10.5 to 11%) obtained with 1:1000 antigen in control series mentioned above may be attributed to the greater amount of protein injected.

Many of the men giving positive skin tests in Group A had had no symptoms of the disease during the 17 months after leaving the endemic area nor during the year of exposure. Such reactions might be thought of as due to a "biological" rather than "clinical" infection; that is, to an infection sufficient to produce skin sensitization but no symptoms, comparable to that observed in certain individuals who give a positive reaction to trichinella antigen. But it is hard to apply this explanation to the incidence in Group B (3 times control series) where the possibility of infection is problematical, and to the rate observed in New Guinea troops (1.6 times control series). Attempts to relate this increased incidence to coincident infection with intestinal helminths have been unsuccessful. At present we have no explanation for this apparent increased skin sensitivity in those who have had tropical service, but it is obvious that it makes the skin test of less value in Group A than is desirable.

Here, then, was a group of over 700 men who were non-effective because of the demonstrated presence of filariasis in a few of them, suggestive physical findings in others, and symptoms without findings but with manifest fear of the disease and anxiety in many more. Others who had been completely symptom-free showed positive skin tests to *D. immitis* antigen. Under current directives those in whom the diagnosis was made were classed as fit only for duty in the Zone of Interior. Since the emotional and psychologic effects of a positive diagnosis was usually much more incapacitating than the manifestations of the disease, and since a positive diagnosis could be made at any time on development of sufficiently characteristic symptoms, it seemed proper to regard only those persons as infected with filaria who presented either a characteristic history of repeated attacks of "mumu," or demonstrable physical signs. Weight was given to a positive skin test, but it alone was not regarded as sufficient for a positive diagnosis. On the other hand a negative skin test did not exclude a diagnosis of filariasis.

After the completion of examination, laboratory studies, and the response to reconditioning, each man's case was appraised. A diagnosis of filariasis was made in those who developed lymphadenitis, especially epitrochlear, axillary, or femoral or funiculitis, epididymitis or orchitis under observation. A retrograde lymphangitis even in the absence of other findings was considered sufficient. A positive diagnosis was also made on a history of one or more clear-cut attacks of "mumu," with swelling, lasting for a day or longer. A history of attacks of pain without swelling, of swelling lasting "a few minutes," of pain in muscles without swelling, or of slight bilateral inguinal adenopathy coming on after a long hike and disappearing with further training, was not considered adequate evidence of filariasis to justify a diagnosis. Nor was the presence of small non-tender axillary, inguinal or femoral glands, which had never given rise to symptoms regarded as acceptable. Such adenopathy was found to be so extremely common by one of us in hospitals in New Guinea as to be of little significance in diagnosis.

A diagnosis of filariasis was made in 196 men (36.8%) in Group A. Of these, 3 were separated from the service because of filariasis—1 with persistent lymph edema of both legs, and 1 with a lymph scrotum, and 1 with recurrent lymphangitis.

A diagnosis of filariasis was also made in 6 men in Group B on the basis of a typical history of "mumu" although no attacks were observed and all had negative skin tests. With the information now available of the questionable presence of a signifi-

cant amount of filariasis on Woodlark Island where they served, it is believed that these diagnoses were incorrect.

Twenty-eight men of Group A were separated from the service or placed on limited duty for other reasons. The remaining 308 were returned to duty as not infected with filaria. Of these, 5 have returned to the hospital for further observation. One of these had had a very equivocal history, negative physical examination, and repeatedly negative skin tests. On re-examination he complained of pains in arms and axillæ without demonstrable swelling, skin test was again negative, and he was again discharged to duty. It is believed that his symptoms are entirely on a functional basis. Another had been admitted to a Station Hospital complaining of pain without swelling in the testes, and pain without swelling in the right thigh. Shortly after admission, he developed infectious hepatitis. On transfer to this hospital he showed only small discrete, non-tender inguinal glands. He was observed for an additional 3 months, including 2 of strenuous reconditioning without further symptoms. It was believed that he did not present sufficient evidence of filariasis to justify the diagnosis, and he was again discharged to duty. Two men had had suggestive histories and positive skin tests when first examined, and on re-examination presented demonstrable adenopathy and were discharged as filariasis. The 5th man showed sufficiently typical symptoms on re-examination to justify the diagnosis of filariasis in spite of repeatedly negative skin tests. In addition to these men, 6 men of Group A and one from Group C have reported on sick call at their present post complaining of swelling of inguinal or, in 1 case, axillary glands. These were not incapacitating and the men returned to duty. Thus follow-up for an additional 8 months has led to a change in diagnosis in approximately 1%.

The histories, physical findings, and skin tests of Group A were again reviewed and separated into those diagnosed as filariasis and as not filariasis. The results, together with similar data for Group B, are shown in Table 6. When the data are assembled in this way, the incidence of a history of swelling of arms, legs or scrotum, and the incidence of positive physical findings in the "not-filariasis" men in Group A and in Group B is strikingly similar. The greater number having positive skin tests in Group A may be an expression of the "biological" infection referred to above. The number of definite attacks of "mumu," so far as could be ascertained, in the 3 groups is shown in Figure 3.

TABLE 6.—INCIDENCE OF POSITIVE HISTORY, PHYSICAL SIGNS, AND SKIN TEST ACCORDING TO DIAGNOSIS

	Group A		Group B
	196 men filariasis (%)	336 men not filariasis (%)	145 men not filariasis (%)
History of swelling arms	55.1	23.5	13.3
legs	42.8	22.9	20.6
scrotum	73.4	35.2	23.4
Axillary adenopathy	49.4	20.8	23.4
Epitrochlear adenopathy	23.9	4.4	4.1
Inguinal adenopathy	75.5	36.6	34.5
Femoral adenopathy	50.5	20.2	19.3
Enlarged epididymis or testicle	14.2	1.7	1.3
Thickened cord	21.9	5.6	5.5
Cervical adenopathy	2.0	1.4	
Positive skin test	79.5	42.0	19.1

Comment. What the future holds for those in Group A who have been infected cannot be predicted with certainty. From Figure 2, it is apparent that the incidence, as well as the severity, of symptoms has rapidly diminished during the past year.

O'Connor and others have reported patients who on return from an endemic area lived the rest of their lives without symptoms. Will these men show microfilariæ in the peripheral blood at a later date? In India, Ivengar[6] found that the incidence of filarial infection (microfilaria in blood) increased from childhood up to the age of 20, and then remained constant, while the incidence of filarial disease, as manifest by symptoms, increased steadily up to the age of 45. That is, microfilariæ were less apt to be found in the blood of those showing symptoms than in those symptomsated for by a ripe anastomosis. The embryos give rise to no trouble, but circulate as easily as blood corpuscles. When in health and not disturbed, they are perfectly inocuous." That the lymphadenitis and lymphangitis of filarial disease are not fundamentally due to secondary bacterial infection has been shown by O'Connor,[8] Wartman[12] and others. These symptoms are in the nature of an allergic response on the part of the host to some antigen derived from dead or living worms, and therefore indicate some degree of immunity. Biopsies of acutely swollen glands and

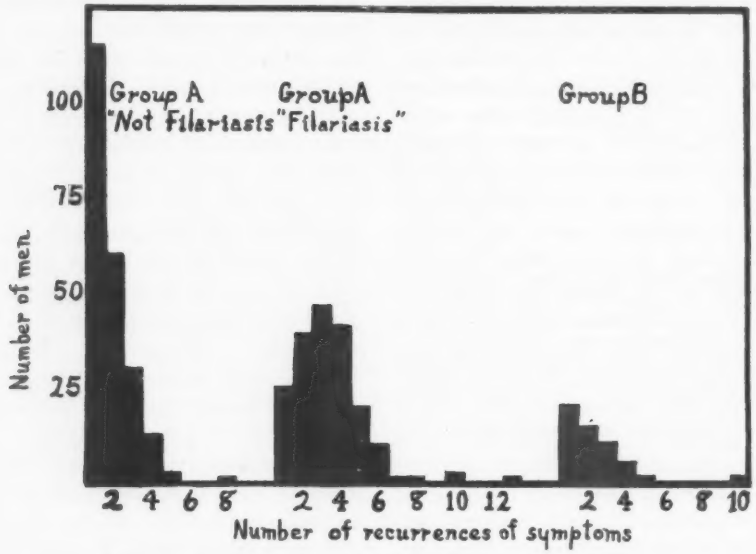

FIG. 3.—Frequency graph of number of attacks of "mumu."

free. This has also been corroborated in many other surveys. Manson[7] in 1883 wrote of Bancrofti infection: "There is nothing in it, or its relation to the human host, incompatible with the perfect health of the latter. The amount of injury done to the lymphatics by the minute, immature parasite in its travel toward its permanent abode is so trivial that no serious disease can possibly result from it. The mature animal itself lies extended in a vessel and is perfectly adapted by size and shape for the situation it occupies. It creates no irritation and the small amount of obstruction it may give rise to is readily compenlymphatics have shown both dead, disintegrating and mature, living worms. Thus even in these early cases some worms are already dead. Others are apparently producing mature microfilariæ. The hypothesis that the failure to demonstrate microfilariæ in the peripheral blood is due to obstruction in glands or lymphatics, and that with the passage of time channels may be opened permitting access to the vascular system appears unlikely. The most obvious explanation for the failure to find microfilaria is the minimal or light infection. It also seems reasonable that some worms will continue to die, and that the

few survivors will live in the innocuous symbiosis described by Manson. With few exceptions it therefore seems reasonable to predict that those men who have these minimal infections will have little further physical disability and less incapacity. Zeligs[13] has presented convincing evidence for this conclusion from a large experience with similar cases of filariasis at the U. S. Marine Barracks, Klamath Falls, Oregon.

One soldier, who served in another endemic area, has been encountered, who has never had any symptoms but shows large numbers of microfilariæ in his blood. It is believed that this, however, is very exceptional, and cannot be used to support the suspicion that a condition may exist among troops similar to that found by Ivengar among natives in India, namely a high incidence of filarial infection without symptoms. If this were so, it is reasonable to suppose that microfilariæ would have been found in the repeated searches in the symptom-free members of Group A. Such, however, was not the case.

A considerable number of troops stationed in certain parts of the Pacific area have been infected with filariasis during this war. Due to the unfamiliarity of most physicians with the early manifestations of the disease, the diagnosis has been made not only in men who have never been in an endemic area, but in many others whose symptoms were due to a variety of causes. Men have been sent to this hospital with a diagnosis of filariasis who suffered from angioneurotic edema, thrombophlebitis, lymphogranuloma venereum, epididymitis secondary to prostatitis or urethritis, and a variety of similar conditions. In our opinion the occurrence of muscle pains, nocturnal orchiodynia or numbness in an extremity, even in men who have been in an endemic area, is not evidence of filarial infection.[10] Too much emphasis cannot be laid on the fear, worry, and anxiety produced in men when the suggestion of possible filarial infection is made. There is fear of a slowly developing, disfiguring and ultimately incapacitating disease. Anxiety for loss of potency or fertility and the possibility of carrying on a normal family life is often extreme. The fact that no specific effective treatment, other than time, has yet been accepted adds to the sense of helplessness and abandonment. Zeligs has presented factual data which shows that these fears are groundless. His data and ours show that in a non-endemic area the disease filariasis burns itself out after one or more reactivations. The longer the period of inactivity because of a diagnosis of filariasis, the more difficult it is to return men to duty. When presented with evidence of their ability to lead normal lives, and the demonstration that they can exercise without producing symptoms most men cease to be concerned. Those with a past history of psychoneurotic behavior, or where the element of secondary gain from light duty was prominent, frequently used filarial symptoms to help solve pre-existing emotional problems or to escape unpleasant situations.

The diagnosis of early filariasis is difficult. Demonstration of microfilariæ or adult worms in biopsy material are the only documentary evidence. The observation of a typical attack of "mumu," with fever, lymphadenopathy and retrograde lymphangitis is convincing. In patients removed from an endemic zone, where diagnosis must be based on history, symptoms, and minimal physical findings, a careful appraisal of all evidence is essential. The skin test is helpful, but eosinophilia or other laboratory examination is of no value. It must be determined whether the man has been in an endemic area. All other discoverable causes for the symptoms should be excluded. The emotional status of the patient must be appraised. When a diagnosis of filariasis is made, sufficient factual data is now available to provide a favorable prognosis. Simple rest for a few days during acute exacerbations, with a prompt return to duty is the proper treatment.

Summary. 1. Observations are reported on 532 men who had spent a year on an island where filariasis was highly endemic.

Sufficient clinical evidence was present to make a clinical diagnosis of filariasis in 36.8%. Microfilariæ were demonstrated in at least 2, and possibly 4, men who had been stationed on this island. Persistent disabling symptoms were present in 3. The recurrence of symptoms, usually precipitated by exertion, diminished with the passage of time. Most men were symptom-free after they had been out of the endemic area 20 months.

2. Observations are also reported on the symptoms and physical findings in 145 men among whom clinical diagnoses had been made, but in whom exposure was problematical.

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THE TREATMENT OF BACTERIAL ENDOCARDITIS WITH PENICILLIN*

RESULTS OF 17 CONSECUTIVE UNSELECTED CASES†

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UP to the time that penicillin was introduced little therapeutic advance had been made in the treatment of bacterial endocarditis although considerable work had been done on this disease both as to pathogenesis and therapy.[8,11,12,13,14,15] The report of Loewe and his associates[17] upon the value of penicillin and heparin opened up new vistas. In our original study it was planned to use heparin with penicillin in half of the cases and penicillin alone in the other half. Our earlier results, presented in a preliminary report,[19,20] were so promising, however, that it was decided to use penicillin alone in all cases without any anticoagulant. The present report deals with a detailed presentation and follow-up of our first 7 cases previously reported and of 10 additional ones treated since then. All cases were *consecutive* and *unselected*, the only requirement being conclusive clinical evidence of bacterial endocarditis and at least two positive blood cultures in our laboratory

The method of penicillin administration, the duration of therapy and other similar comments are presented in the discussion which follows the data of the individual cases. The data is presented in the following case reports and is summarized in Table 1.

Case Reports. CASE 1. P. H., a 60 year old female with a history of "heart trouble" since 1939, was admitted to this hospital for terminal care on May 25, 1944 before our study began. A diagnosis of subacute bacterial endocarditis had been made at another institution and the patient had failed to respond to treatment with sulfadiazine and typhoid vaccine. The diagnosis of subacute bacterial endocarditis was substantiated by us before treatment was begun. There were petechiæ in the conjunctival sacs, a moderately enlarged heart, aortic and mitral valvular involvement, an enlarged spleen, a temperature of 104° F., and repeated positive blood cultures for *Streptococcus viridans*. The qualitative tests showed the organism to be penicillin sensitive. The patient was given 200,000 units of penicillin by continuous intravenous drip which had to be discontinued after 12 days because of thrombophlebitis and lack of accessible veins. The intramuscular route every 2 or 3 hours was then employed for the remaining 9 days. Five days after completion of the first course, the blood culture revealed a few chains of streptococci which resisted subculture. A second course of 21 days of intermittent intramuscular penicillin was given and the patient then made an uneventful recovery. During treatment, a diastolic murmur over the aortic area became clearly audible for the first time and peripheral signs of aortic insufficiency became apparent. With control

* The penicillin for 15 cases was provided by the Office of Scientific Research and Development from supplies assigned by the Committee on Medical Research for clinical investigations recommended by the Committee on Chemotherapeutics and Other Agents of the National Research Council. Penicillin for Case 17 and part of the penicillin for Case 13 was supplied by Commercial Solvents, Inc.

† Aided by the Herbert G. Mayer Fund for Cardiovascular Research. The Cardiovascular Department is supported in part by the Michael Reese Research Foundation.

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TABLE 1.—DATA OF 17 CASES OF SUBACUTE BACTERIAL ENDOCARDITIS TREATED WITH PENICILLIN ALONE

Case	Age and Sex	Cardiac diagnosis and probable duration of infection (weeks)	Previous treatment	Penicillin: Sensitivity units per cc. test broth	Penicillin: Daily usage (units × 1000) and route	Penicillin: No. days therapy	Penicillin: Total units millions	Penicillin: Blood serum level* (units)	Complications	Follow up (months)† and result	Remarks
1. (P. H.)	60 ♀	Rh A.R. M.D. (16)	Sulfadiazine, typhoid vaccine	Qualitatively sensitive	200 iv drip 25 q.3hr.im 8.3 q.2hr.im 4.2 q.2hr.im 16.6 q.2hr.im (intermittent)	12 8 8 7 21 56	9.3		Thrombophlebitis	(20) Recovered	Mild congestive heart failure. Controlled with digitalis and diuretics.
2. (W. L.)	36 ♂	Rh. A.R. M.D. (5)	None	Qualitatively sensitive	200 iv drip 8.3 q.hr.im 4.3 q.hr.im	8 14 14 36	5.6	0.06	Thrombophlebitis	(20) Recovered	Working. No medication.
3. (R. B.)‡	6 ♂	None (3)	Sulfonamides 100,000 units of penicillin	0.04	8.3 q.hr.im 11.1 q.2hr.im	7 14 21	4.2	0.96 0.08	Urticaria Hay fever	(18) Recovered	Attends school.
4. (W. G.)	51 ♀	Rh. M.S. (10)	None	0.02	8.3 q.hr.im	21	4.2	0.16		(18) Recovered	Doing housework. Moderate congestive failure.
5. (O. M.)	19 ♀	Cong. Rh. P.D.A. A.R. (16)	Sulfadiazine (for pneumonia)	0.04	8.3 q.hr.im	42	8.1	0.12	Multiple pulmonary infarcts. Infectious mononucleosis	(16) Recovered	Precordial distress.
6. (S. K.)	45 ♂	Rh. A.R. M.D. (13)	4.5 million units of penicillin	0.06	8.3 q.hr.im 200 im drip 300–400 iv drip 300–500 iv drip + q.2hr.im 400 im drip 16.6 q.hr.im 1000 iv and im drip (intermittent)	22 22 26 73 15 158	57.0	0.24 0.29 0.60 0.16	Septic lung infarcts with empyema. Bacteroides septicemia Rib resection. Glomerulonephritis.	(1) Relapsed 20 days after last course and died at home shortly thereafter. No autopsy.	Treatment failure.
7 (H. W.)	50 ♀	Rh M.D. (12)	None	0.04	16.6 q.hr.im 8.3 q.hr.im 4.6 q.hr.im	1 42 3 46	9.1	0.24	Essential hypertension. Rheumatoid arthritis.	(15) Recovered	Doing light housework.
8. (M. H.)	35 ♀	Rh. M.D. (20)	None	0.04	8.3 q.hr.im	21	4.2	0.06	*E. histolytica* carrier	(15) Recovered	Palpitations due to premature systoles.
(E. F.)		A.R. M.D. (9)			16.6 q.hr.im 16.6 q.hr.im 400 iv drip + 4.6 q.hr.im (alternating) 20.8 q.hr.im	13 14 5		0.24 0.64	[illegible]	Readmitted and died in congestive heart failure.	[illegible] bolus to posterior tibial artery. Necropsy evidence of healing and healed valvulitis.

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						46	9.1				ritis.
S. (M. H.)	35 ♀	Rh. M.D.	None	0.04	8.3 q.hr.im	21	4.2	0.06	*E. histolytica* carrier	(15) Recovered	Palpitations due to premature systoles.
		A.R. M.D. (9)			12.5 q.hr.im 16.6 q.hr.im 400 iv drip + 4.6 q.hr.im (alternating) 20.8 q.hr.im	13 14 5		0.24 0.04		Meningism; died in congestive heart failure.	Embolus to posterior tibial artery. Necropsy evidence of healing and healed valvulitis.
						46	16.8				
10. (A. R.)	22 ♀	Cong. I.V.D. (6)	None	0.03	8.3 q.hr.im	18	3.6	0.12		(14) Recovered	No medication. Doing housework.
11. (E. B.)	22 ♀	Cong. I.V.D. (4)	Sulfadiazine	0.03	8.3 q.hr.im	21	4.2	0.06	Pulmonary infarcts	(13) Recovered	Returned to hospital with petechiæ; no evidence of recurrence. Occasional petechiæ since.
12. (R. S.)	12 ♂	Cong. I.V.D. (17)	None	0.03	12.5 q.hr.im 8.3 q.hr.im 4.6 q.hr im	2 20 3		0.04		(13) Recovered	Returned to school.
						25	4.9				
13 (S. H.)	38 ♂	Cong I.V.D. (16)	5 million units of penicillin	0.03	12.5-20.8 q.hr.im 12.5-20.8 q hr.im 500 iv and im drip 1200-3000 iv and im drip	25 92 28		0.20 0.16 1.5-5.0§	*A. lumbricoides* infection Thrombophlebitis	(10) Recovered	Working. No medication.
						145	112.3				
14. (R. M.)	40 ♂	Rh. Bicusp. Aortic valve M.D. (44)	Sulfapyridine, sulfadiazine, 500,000 units of penicillin	0.08	12.5 q.hr.im	13	3.9		Congestive heart failure. Hypoproteinemia	Died	Post-mortem blood sterile *Strep. viridans* cultured from valve.
15. (A. B.)	27 ♂	Rh. A.R. A.S. M.D. (40)	Sulfadiazine 3 million units of penicillin	0.02	12.5 q.hr.im 16.6 q.hr.im 300-400 im drip	22 5 8		0.08 0.20		Died	Cerebral hemorrhage. Splenic "abscess" with mycotic aneurysm of splenic artery. *Strep. viridans* cultured from aortic valve.
						35	11.4				
16. (E. R.)	21 ♀	Rh. A.R. M.S. (3)	None	0.015	8.3 q.hr.im 12.5 q.hr im 16.6 q.hr.im	34 5 17		0.04 0.08	Pregnancy and hysterectomy	(12) Recovered	Petechiæ post-therapy. Doing housework, afebrile, cultures sterile.
						56	15.1				
17. (M. B.)	15 ♀	Rh. M.D. A.R. (8)	None	0.06¶	10.0 q.hr.im 8.3 q.hr.im 16.6 q hr im 20.8 q.hr.im 1000 im drip 2000 im drip	3 5 6 41 14 7	52.6	0.30		(8) Recovered	Congestive failure and auricular fibrillation has developed.
						76					

* Refers to units of penicillin per cc. of serum just preceding the next injection. It represents the lowest concentration of penicillin in the injection period.

† As of March 1, 1946.

‡ Only case with *Strep. hemolyticus*. All others were *Strep. viridans*.

§ When 6% para-aminohippuric acid was used in combination with 2.5 million units of penicillin intravenously.

¶ Kindly redetermined for us by Dr. L. Loewe of Brooklyn Jewish Hospital.

A.R. = aortic regurgitation
M.D. = mitral disease
M.S. = mitral stenosis
A.S. = aortic stenosis

Rh. = rheumatic
Cong. = congenital
I.V.D. = interventricular septal defect
P.D.A. = patent ductus arteriosus

of the sepsis, mild conjestive heart failure appeared which was easily controlled by the usual cardiac régime. The patient was discharged 15 weeks after admission as arrested. She has had no recurrence for 20 months and is gainfully employed as a dressmaker. Her mild heart failure is adequately controlled with digitalis.

The patient was readmitted March 3, 1945 with a pneumococcus (Type 19) infection of the right lower lobe, without any recurrences of the bacterial endocarditis. Several blood cultures were taken at this time which were consistently negative for *Strep. viridans* or other bacteria.

Case 2. W. L., a 36 year old male with a rheumatic history since childhood but with little cardiac disability was admitted on May 4, 1944, with chills, fever, malaise and generalized weakness of 2 weeks duration following an upper respiratory infection. Examination showed the presence of mitral and aortic valvular involvement. Four blood cultures were positive for *Strep. viridans*. Qualitative tests showed the organism to be penicillin sensitive. There was consolidation in the right lower lobe, believed to be due to pulmonary infarction. The patient was given 200,000 units of penicillin by continuous intravenous drip for 8 days. The temperature which had fallen to normal levels at the onset of treatment rose again during treatment and blood cultures became positive. The route of therapy was changed and 8300 units were given intramuscularly every hour on the hour day and night for 2 weeks; then 4300 units were given per dose in the same manner for an additional 2 weeks. The temperature promptly dropped and the patient made an uneventful recovery. He was discharged from the hospital June 30, 1944 and has been back at his former occupation. He has been asymptomatic and has had no recurrence for 20 months.

Case 3. R. B., a 6 year old male, with no previous history of, or findings indicating, congenital or rheumatic heart disease, but with a history of hay fever and allergic food idiosyncrasies developed a rise in temperature to 106° F. 1 day after tonsillectomy. He was given sulfanilamide and sulfadiazine and 100,000 units of penicillin at another institution after a blood culture containing a hemolytic streptococcus was obtained. The response was not satisfactory. On admission, on Aug. 10, 1944, the temperature was 106° F. The child was dehydrated and drowsy. Two blood cultures were positive for *Strep. hemolyticus*, sensitivity 0.04 Oxford units of penicillin. A harsh, systolic murmur at the apex was present with transmission towards the axilla. The family physician stated that no murmur was present previous to the present illness. During treatment, the murmur became more blowing and higher pitched. The heart was of normal size on Roentgen ray and fluoroscopy. The urine was normal on microscopic examination and sterile on culture. The tonsillar fossæ were healed. The child was given 8300 units of penicillin intramuscularly every hour day and night for 1 week. Because of the high blood serum levels obtained and because of the immediate rapid favorable response, he was then given 11,100 units intramuscularly every 2 hours for the next 14 days. The child developed a generalized urticaria on the second day of treatment, which responded to symptomatic treatment. The blood cultures soon became sterile. The patient was sent home symptom free on the 38th day. He has returned to school, has had no recurrence for 18 months and is carrying on normal activity. A residual soft systolic blowing murmur at the apex has disappeared.

Case 4. W. G., a 51 year old woman, with a vague history of rheumatic fever in 1906, was admitted on Aug. 11, 1944 with fever and weakness of 10 weeks duration. On May 15, 1944, the patient had a tooth extracted and was given sulfathiazole prophylactically. On June 3, a second abscessed tooth was extracted but no sulfonamide was given because the patient was nauseated after the previous sulfathiazole administration. Two days following the tooth extraction the patient became febrile. Three blood cultures were positive for *Strep. viridans*, sensivitity 0.02 Oxford units. On examination, the patient had a café-au-lait color, a temperature of 104° F., a palpable, soft and tender spleen, an enlarged heart with an apical presystolic murmur. Starting on the 9th hospital day, 8300 units of penicillin were given intramuscularly every hour day and night for 21 days. The response was dramatic and complete. The patient was sent home on the 38th day. At present, she is doing light housework with only slight cardiac disability. She has had no recurrence for 18 months.

CASE 5. O. M., a 19 year old girl with a past history of congenital heart disease and congenital syphilis. She had received intensive bismuth and arsenical therapy. One week following extraction of an abscessed tooth, she began to have chills and fever. The patient was treated at another institution with sulfadiazine with no response. On admission on Aug. 23, 1944, the girl was acutely ill, with pain in the right lower chest. On examination, there was consolidation of the right lower lobe, a "machinery-like" murmur heard best in the pulmonic area and a questionable early diastolic high pitched murmur heard best at Erb's point. Three blood cultures were positive for *Strep. viridans*, the sensitivity was 0.04 Oxford units. On the 3rd hospital day, the patient was given 8300 units of penicillin intramuscularly every hour day and night. There was a dramatic response in temperature and "clinical well-being" within 48 hours. At the end of 2 weeks, at which time the lung had almost completely resolved, the patient developed a pharyngitis with cervical lymphadenopathy and the temperature rose to as high as 102° F. over the next 6 days. Several blood smears showed mononuclear cells characteristic of infectious mononucleosis. The heterophil agglutination test was positive in the dilution of 1 to 32. Intramuscular penicillin therapy was continued for 6 weeks. It is interesting that the blood cultures remained sterile for *Strep. viridans* during the concurrent infectious mononucleosis. The diastolic murmur at the base became more audible and a diagnosis of aortic insufficiency in addition to a patent ductus arteriosus was made. During treatment, several abscessed teeth were removed* and the sockets packed with penicillin (5000 Oxford units per cc.) soaked sponges. Culture of the sockets before packing revealed *Strep. viridans* predominating. The patient was discharged on the 53rd day after admission. At present the patient experiences mild dyspnea on moderate exertion as well as precordial distress, but has had no recurrence for 16 months. Ligation of the ductus is not contemplated because of the concomitant aortic valvular defect.

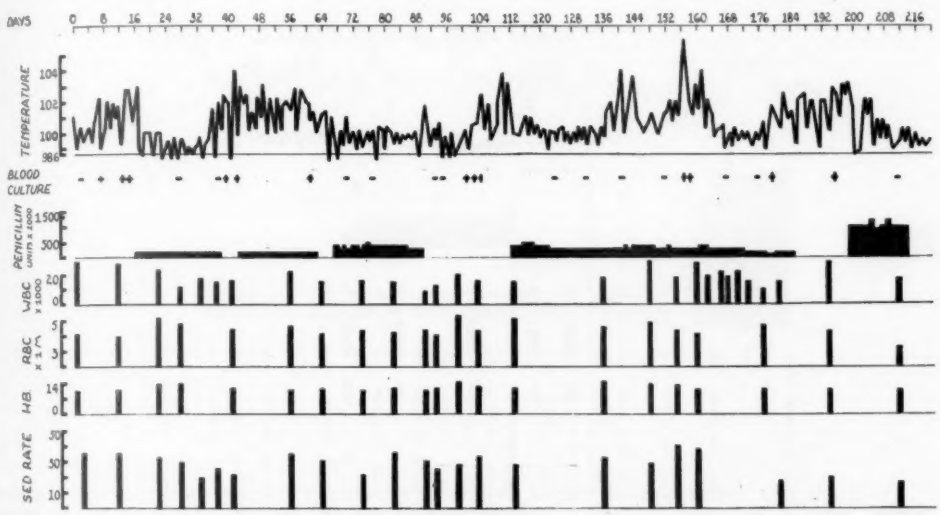

FIG. 1.—Course during hospital stay of Case 6. This illustrates a treatment failure due to organism resistance, embolic complications and inadequate penicillin dosage.

CASE 6. (Fig. 1.) S. K., a 45 year old man, was admitted on Aug. 24, 1944, from another institution, where a diagnosis of acute endocarditis was made because of 4 positive blood cultures for *Strep. hemolyticus*, the presence of aortic and mitral valvular disease, and embolic phenomena. In May, 1944, he had had several teeth pulled and soon thereafter he had weakness, malaise,

* The oral surgery on this and our other patients was performed by Dr. M. Falstein.

and fever. He had previously received a total of 4.5 million units of penicillin by the intramuscular route, administered every 3 to 4 hours. There was no previous history of rheumatic infection or cardiac disability. Physical examination showed evidence of moderate weight loss, aortic and mitral valvular involvement, embolic phenomena, a palpable spleen and slight clubbing of the fingers. The first blood culture was negative, but three taken subsequently were positive for *Strep. viridans*, sensitivity was 0.06 Oxford units. On Sept. 9th, the patient was started on 200,000 units of penicillin per day at the usual concentration, 8300 units intramuscularly every hour during the 24 hour period. This was continued for 3 weeks. The initial response was good. The blood level of penicillin was 0.24 units at the end of 1 hour. On the last day of the 3 week treatment, his temperature spiked and the blood culture was positive. The patient was started on a second course of therapy on Oct. 5th, at the same total daily dosage of penicillin, but by continuous intramuscular drip. The temperature did not reach normal levels at any time during this course, and he began to vomit, necessitating parenteral nutritive therapy for 1 week. There were numerous petechiæ and the vomiting was believed to be of central origin. The blood culture was positive during this course of treatment. A third period of treatment of 26 days was begun on Oct. 30th, using 300,000 to 400,000 units daily by continuous intravenous drip. The temperature responded slightly and embolic phenomena were almost constant although the blood stream was sterilized. However, 6 days after this course of therapy was ended the blood culture was again positive for *Strep viridans*, which still showed the same sensitivity, *viz.*, 0.06 Oxford units. A fourth uninterrupted course of therapy of 73 days was begun on Dec. 12th, employing from 300,000 to 500,000 units daily. This was given by continuous intravenous drip augmented by intramuscular injections every hour for several days; then by alternating continuous intramuscular injections. Renal and splenic emboli were common. Renal studies showed a fixed specific gravity and a urea clearance 30% of normal. The blood chemistry was at the upper limits of normal as were circulation time studies. Several infected teeth were removed. The sockets on culture showed *Strep. viridans*, and they were packed with penicillin. On Dec. 26th, the patient's temperature spiked to 106° F. and there were signs of fluid in the right chest. Blood culture was positive for *Strep. viridans* and Gram negative pleomorphic anerobic non-spore bearing bacillus which morphologically and culturally resembled *Bacteroides funduliformis*.[10] Chest tap revealed foul-smelling pus with the presence of the two organisms described. Thoracotomy and rib resection was done by Dr. R. Bettman. Large quantities of pus in locu-

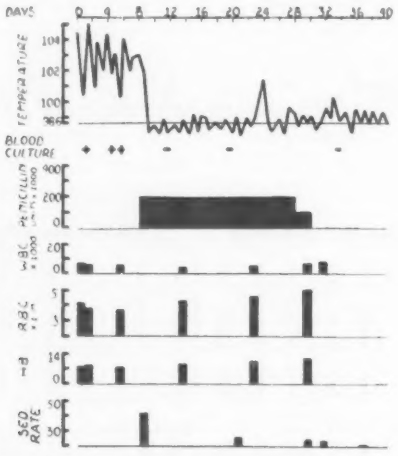

FIG. 2.—Course during hospital stay of Case 8. This illustrates the rapid and sustained response which many of the patients showed. The temperature rise on the 25th day was due to a transfusion reaction.

lated spaces in the pleural cavity were removed and the pleural space drained. The chest cavity was irrigated daily with surface active azochloramine followed by instillation of 30,000 to 50,000 units of penicillin. Because of the concomitant bacteroides infection, which could not be inhibited by penicillin *in vitro*, a total of 88 gm. of sulfanilamide and sulfadiazine were given over a period of 2 weeks postoperatively. The sulfadiazine blood level was 9.5 mg. %. Several transfusions and amino acid infusions were administered. Six days before therapy was stopped, the patient had a positive blood culture for *Strep. viridans*. Because of the recurrence of bacteremia when therapy was stopped, the rising temperature, and the ever present leukocytosis after this extensive treatment, we thought it was useless to continue treatment and called this patient a treatment failure. When penicillin became more readily available, a fifth course of treatment was nevertheless begun, using 1 million units daily by the continuous intramuscular drip for 15 days, supplemented by two daily interrupted intramuscular injections of 100,000 units given 20 minutes apart, during the last 10 days of therapy. The temperature gradually fell to normal and the blood stream remained temporarily sterilized after stoppage of therapy. The thoracotomy wound was now practically healed. After a hospital stay of 221 days and treatment for 158 days, using a total of 57 million units of penicillin, this patient was sent home. Unfortunately, 3 weeks after treatment was stopped, his blood culture again became positive. Shortly thereafter the patient died in his sleep while at home. Autopsy permission was not obtained.

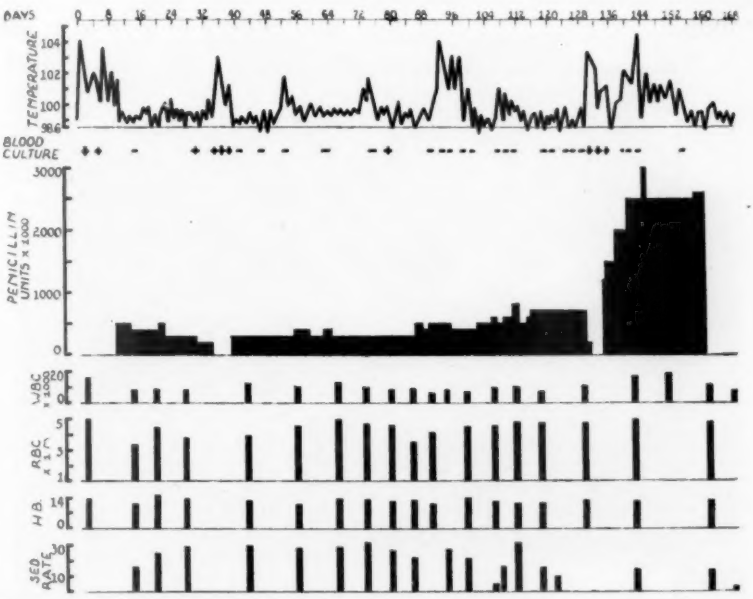

FIG. 3.—Course during hospital stay of Case 13. This illustrates the successful outcome of a resistant case when the penicillin dosage was increased. The temperature rises are due to the recurrent bacteremia when penicillin was stopped or to multiple pulmonary infarcts during the treatment period.

CASE 7. H. W., a 50 year old woman with a history of essential hypertension of 10 years duration with no renal impairment and painful swellings of the interphalangeal and metacarpophalangeal joints, was admitted on Sept. 31, 1944 with the generalized complaints of weakness and anorexia of 3 months duration, chills and fever, and painful swelling of the dorsum of right foot of 4 days duration. Examination showed several conjunctival petechiæ, a typical Osler node on the dorsum of the right foot, enlarged heart with mitral presystolic murmur and other evidence pointing to mitral involvement. Several blood cultures were positive for *Strep. viridans*, the sensitivity was 0.04 Oxford

units. The patient received the now established 3 week course of penicillin, 8300 units intramuscularly every hour day and night. The temperature did not return to normal, during therapy, although blood cultures were sterile. A second similar course of penicillin was therefore given and the response to this was good, although the patient continued to have typical Osler nodes on the thenar and hypothenar eminences of both hands which gradually disappeared. The patient was discharged 75 days after admission. The sedimentation rate did not return to normal until several weeks after the patient was discharged. She is now doing light housework and has had no recurrences for 15 months.

drop in temperature and clinical "well-being" occurred within 36 hours. On the 25th treatment day, the temperature rose to 101.4° F. because of a transfusion reaction. Stools were positive for *Endamœba histolytica* and a course of carbarsone was given. Subsequently to this stool study has been negative. Prophylactic extraction of several teeth was performed during the penicillin treatment period without untoward effects. The patient was discharged on the 40th hospital day asymptomatic. This patient showed a rapid and complete response to treatment—the café-au-lait color disappeared, the hemoglobin (which was 7 gm.% on admission) had returned to normal on discharge, the

FIG. 4.—Case 15. Close-up view of aortic valve and anterior leaflet of the mitral valve showing friable vegetations on the right and non-coronary cusp of aortic valve. Vegetations on chordæ tendineæ showed almost complete healing by organization and regrowth of endothelium. No bacteria were present. Vegetations on the left coronary cusp showed healing with no colonies of bacteria present. Note perforation of anterior mitral leaflet.

CASE 8. (Fig. 2.) M. H., a 35 year old woman with a history of heart disease since the age of 16, was admitted on Oct. 12, 1944 with the complaints of fever and weight loss of 6 months duration. Examination revealed a typical café-au-lait color, petechiæ in the left conjunctival sac, marked splenic enlargement, and enlarged heart with evidence of a mitral stenosis, and a temperature 104° F. The blood cultures were repeatedly positive for *Strep. viridans*, the sensitivity was 0.04 Oxford units. The patient was given 8300 units of penicillin intramuscularly every hour for 21 days. A precipitous sepsis had rapidly disappeared, and her personality quickly changed from complete negativism to coöperativeness and sociability. Since discharge, she has been doing housework and has had no recurrence for 15 months.

CASE 9. E. T., a 36 year old male Negro with a history of syphilis 15 years before, for which he had received irregular treatment for about 2 years, was admitted on Oct. 25, 1944, with the complaints of painful finger tips, epistaxis, headaches, migratory joint pains, chills, and fever of 9 weeks duration. Examination showed several pete-

chiæ in the conjunctival sacs, Osler nodes on the finger tips, markedly enlarged heart with aortic insufficiency and mitral valvular involvement. The left knee and right ankle were swollen, hot and tender, temperature 102° F. The electrocardiogram showed prolongation of the P–R interval to 0.30 second. The blood cultures were positive for *Strep. viridans*, the sensitivity was 0.04 Oxford units. He received 8300 units of penicillin intramuscularly every hour day and night for 10 days during which time the chills and fever continued, petechiæ were numerous, and subungual splinter hemorrhages appeared. Continuous intramuscular and intravenous drips were then started employing 200,000 to 400,000 units of penicillin daily. Embolic phenomena were almost continuous. Several abscessed teeth were removed and the routine of packing of the sockets with penicillin employed. No untoward effects were observed. During the last 5 days of treatment, 500,000 units daily were used by the hourly intramuscular route. The temperature gradually fell to normal. Two days before penicillin was stopped because of the then unavailable supply, he had a new crop of petechiæ. He received a total of 16.8 million units of penicillin during 46 continuous treatment days. The prolonged A–V conduction time returned to normal within a month. The Wassermann, Kahn and Eagle reactions, which were positive before treatment did not change qualitatively or quantitatively after treatment. Near completion of therapy, signs of cardiac insufficiency developed and paroxysmal dyspnea was common. Digitalization did not improve his symptoms but periodic mercurial diuretics were helpful. He was discharged on the 94th hospital day.

Two weeks following discharge, and 9 weeks after penicillin was stopped, he complained of sudden pain in his left foot. Examination showed absent pulsations in the left dorsalis pedis and posterior tibial arteries, swelling and coldness of the left foot. Repeated blood cultures were sterile. On vasodilators and symptomatic treatment, pulsations returned, edema subsided, and the patient made an uneventful recovery. This episode was interpreted as a sterile embolization to the posterior tibial artery. He later developed a peculiar musical diastolic murmur over Erb's point. Although this case was complicated by positive Wassermann and Kahn tests, and posttreatment sterile embolization, the patient made a good recovery from his subacute bacterial endocarditis and there had been no evidence of

FIG. 5.—Case 14. Heart showing ulceration and fragmentation of bicuspid aortic valve. Vegetations revealed *Strep. viridans* on culture.

its recurrence until the patient's death, 8 months later. The patient, however, developed moderate congestive failure, and required digitalis, mercurials and restriction of activities for its control.

He was readmitted to the hospital on June 18, 1945, 6 months after he had been discharged following successful penicillin therapy) because of progressively increasing congestive heart failure. All attempts to control his heart failure were unsuccessful. He died on Aug. 26, 1945 (8 months after penicillin therapy had been successfully used). Blood cultures during this admission were repeatedly negative.

grayish streaks throughout. The wall of the right ventricle measures 0.5 cm., that of the left ventricle 1.4 cm. There is a red slightly attached thrombus at the appendage of the right auricle. Several yellowish gray, moderately firm thrombi are attached to the endocardium of the right ventricle. They measure up to 2 cm. in greatest dimension. The endocardium of the left auricle, just above the mitral valve, shows several firm, grayish, smooth projections and whitish striæ. The tricuspid and pulmonic valves show no gross changes. The severely disfigured aortic valve shows a thickening and rolling of the free margins with a hyaline plaque (6 mm. in diameter) projecting from the intima of the

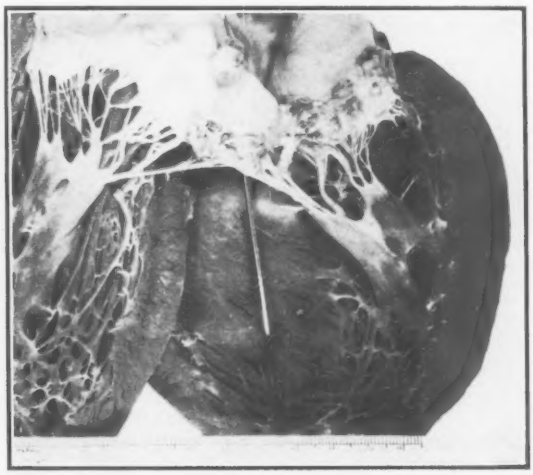

FIG. 6.—Case 14. Heart showing aneurysm formation with perforation of the anterior mitral leaflet. There are many vegetations on both leaflets of the thickened scarred valve.

AUTOPSY revealed: healed subacute bacterial endocarditis of the mitral and aortic valves with a perforated aneurysm of the mitral valve, aortic valvulitis, syphilitic aortitis involving the aortic valve and encroaching on the mouth of the right coronary artery, pulmonary embolus with infarction and chronic passive hyperemia. There were no fresh vegetations present. The important gross and histological findings are illustrated in Figures 7 to 14.

The following pertinent data are from the pathologist's report:

Gross Description of Heart. The heart is moderately enlarged (450 gm.) and is moderately dilated in all chambers. The pericardium is smooth and glistening. The myocardium is firm, brown, and shows a few

aorta and separating the commissures, between the right and posterior cusps. It had also encroached upon the mouth of the right coronary artery. The plaque measures about 6 mm. in diameter. The posterior cusp is markedly shortened, the noduli Arantii are displaced towards the commissure, and it exhibits a perforation 4 mm. in diameter. The aortic ring is distinctly dilated, measuring 9 cm. in circumference.

The aortic leaflet of the mitral valve contains a broad aneurysmal outpouching (2 × 3 cm.), with a 3 mm. perforation (see Fig. 6). The auricular surface of the lesion and of the remainder of the valve is smooth and glistening; the ventricular surface is roughened with the outpouchings separated by slender bands of scar tissue. However, no

recent vegetations are present. There is no obvious thickening of the line of contact of the valve apart from the aneurysm. One chorda tendineum of the aortic leaflet is moderately thickened; the rest are delicate. The roughening due to the scar tissue extends to the aortic valve on the endocardium of the left ventricle.

The mitral valve measures 8 cm., the pulmonic 7 cm., and the tricuspid 13 cm. in circumference. The mural endocardium of the interventricular septum of the left ventricle, and especially just beneath the aortic valve, discloses a diffuse, whitish thickening. In one region, close to the attachment of the aortic leaf of the mitral valve, there is a small, roundish, whitish defect, 3 mm. in diameter, which leads into a shallow, smooth-walled cavity. Some of the thickened areas have produced pockets, their opening directed either towards the aortic valve or towards the apex of the heart.

The aorta has lost some elasticity. In its ascending portion, close to the sinus of Valsalva, the endocardium discloses a number of reddish plaques and horizontally placed wrinkles with red bases, also areas of hyalinization and foci of fatty degeneration. The mouth of the right coronary artery is distinctly narrowed; that of the left is patent; they show only a moderate arteriosclerosis.

Microscopic Examination. *Mitral Valve.* In some fields there is a marked thinning of the substance of the valve with some new fibroblasts and infiltrated lymphocytes. Adjacent areas show moderate hyalinization. In other fields there is a rich infiltration of lymphocytes and monocytes with newly formed blood vessels. At the most distal part of the aortic leaf of the mitral valve small foci of necrosis are encountered, surrounded by monocytes and lymphocytes. Other sections show, at the periphery of this leaflet, an obvious new formation of lining endothelial cells with hyperchromatic nuclei. Occasionally some of the monocytes are heaped up and project over the surface. In other sections again, attached to the surface of the valve, there are a few projections consisting of young connective tissue cells with a few scattered lymphocytes. Occasionally, a few areas of dark bluish stained, granular material can be made out. Special stains show this to consist of calcium and intermingled Gram positive cocci.

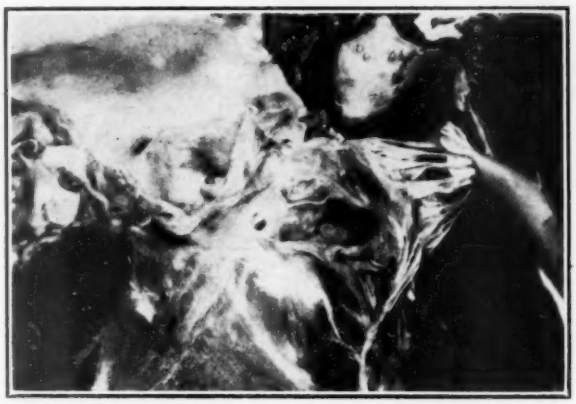

Fig. 7.—Case 9. Aortic valve and aortic leaf of the mitral valve. Note the narrowing of the mouth of the right coronary artery, the hyalinized plaque with horizontal wrinkling of the aorta, the separation of the commissure and the rolling and thickening of the aortic cusps. Also note the saccular cavity in the aortic leaf of the mitral valve.

Aortic Valve. The free margins of the aortic cusp show a new partly hyalinized connective tissue containing minute elastic lamellæ, a moderate infiltration of lymphocytes, and insignificant foci of necrosis. The midportion of the cusp is somewhat thicker than normal and its ventricular surface contains new connective tissue cells and fibers with a number of lymphocytes and rare neutrophils. Close to the base of the valve there are occasionally found small projections consisting of many spindle-shaped nuclei, surrounded by one layer of flat epithelial cells. The free margins of the cusps disclose centers of necrosis surrounded

by connective tissue fibers with a large number of elastic lamellæ. The base of the sinus of Valsalva shows a new formation of blood vessels, some of which are surrounded by lymphocytes.

Aorta. There is, in many fields, an interruption of the elastic lamellæ of the media. The adventitia in corresponding areas shows a perivascular infiltration of lymphocytes of varying degrees associated with a thickening of the walls of the vasa vasorum and diffuse fibrosis.

lamellæ of the media, the marked thickening of the adventitia with perivascular round cell infiltrations, are characteristic. The older inflammation in the cusps (new formed connective tissue with scattered lymphocytes and a few monocytes) is obviously not associated with the syphilitic process. The organized and healing vegetations are lined by regenerated endothelial cells. It is perhaps significant of the type of the inflammatory changes that the adjacent portion of the septal endocardium shows similar

FIG. 8.—Case 9. Mitral valve (auricular aspect). Note the bulging aneurysm and the perforation.

Sections taken from the uppermost portion of the interventricular septum, just beneath the aortic valve, shows the endocardium covered by much old granulation tissue with many spindle-shaped nuclei. Very rarely an occasional neutrophil is encountered.

Myocardium. Within the myocardium there are many fields where the muscle fibers are interrupted by minute healed infarcts (old scar tissue containing a number of blood vessels). There are also small areas of fibrosis, especially in perivascular regions. Here and there small foci of lymphocytes, monocytes, and plasma cells are present in the perivascular spaces. Nowhere is there any evidence of Aschoff bodies.

Summary of the Heart Findings. Significant changes were found in the aortic and mitral valves. The basic lesion of the aortic valve is obviously syphilitic aortitis which had extended into the sinus of Valsalva. Grossly, the separation of the commissures, the presence of a hyaline plaque at the region of the commissures and the narrowing of the mouth of the coronary artery, are pathognomonic. Histologically, the interruption of the elastic

changes. This suggests that the acute inflammatory lesions had extended from the aortic valve to the mural endocardium—a common finding in acute and subacute bacterial endocarditis.

The mitral valve lesions are unusual. Outstanding were the thinning and bulging of the aortic leaf of the mitral valve with perforation, the bulge directed towards the auricle. The cause for the bulge, as clearly seen in the histologic section, is an older valvulitis which had caused the thinning, *i. e.*, a mycotic aneurysm. Evidence is also present of a diffuse valvulitis in the healing and healed stage with many connective tissue cells, a few lymphocytes and only very few neutrophils. In one region, close to the free margin foci of necrosis with a few bacteria (or stained precipitate) are still encountered. It is important that these areas were completely surrounded by connective tissue cells and fibers, and that the free surfaces of the leaf were covered by apparently regenerated endothelial lining cells. No cultures were made of these areas.

The myocardium showed multiple minute

infarcts with many foci of fibrosis and rare small areas of localized subacute and chronic myocarditis. Nowhere in the sections was anything found that could be interpreted as remnants of Aschoff bodies.

Thus, it is clear that this is a case of a syphilitic aortitis and aortic valvulitis with insufficiency. It is also evident that an acute or subacute bacterial endocarditis had been superimposed upon the syphilitic process. This was definitely in the healing and healed stage. Because the endocarditis was superimposed upon an older (syphilitic) lesion, because it had extended to the adjacent mural endocardium and endocardium of the mitral valve, and because throughout the myocardium multiple small infarcts were encountered, it is safe to assume that the endocarditis must be classified, from the morphologic standpoint alone, as subacute bacterial endocarditis. The patient died as a result of myocardial failure. This is a complication of arrested subacute endocarditis.

FIG. 9.—Case 9. Healing vegetation, aortic valve. Note the regenerated endothelial lining cells. Orcein preparation; × 45.

FIG. 10.—Case 9. Mitral valve. Note the rich granulation tissue. Iron-hematoxylin-eosin preparation; × 125.

CASE 10. A. R., a 22 year old woman with a history of congenital heart disease and "slow pulse" was admitted on Nov. 7, 1944 because of unexplained fever of 6 weeks duration. On examination, there was a subungual splinter hemorrhage, an enlarged heart, a long, rough systolic murmur present over the entire precordium, parasternally, with varying intensity of the first heart sound from cycle to cycle with jugular pulsations at times other than that of the first heart sound. The pulse varied from 50 to 64, although the temperature was 103° F. The electrocardiogram showed complete A–V heart block. Blood cultures were positive for *Strep. viridans*, the sensitivity was 0.03 Oxford units. The patient was given 8300 units of penicillin intramuscularly every hour day and night. Clinical improvement was rapid and maintained. Laboratory studies corroborated the clinical impression. Treatment was stopped on the 18th day and the patient was discharged on the 33rd hospital day, asymptomatic. She is back at her former occupation and has had no recurrence for 14 months.

CASE 11. E. B., a 22 year old woman, followed since birth at another hospital with a diagnosis of patent interventricular septum, was admitted Nov. 20, 1944, with fever, blood streaked sputum and generalized weakness, of 4 weeks duration. She had been treated at home with sulfadiazine with no improvement. Examination revealed an enlarged heart, a systolic thrill, a loud rough systolic murmur (best heard in the 5th intercostal space parasternally), and consolidation in the right lower lobe. The temperature was 102.8° F. Blood cultures were positive for *Strep. viridans*, the sensitivity was 0.03 Oxford units. The patient was given 8300

units of penicillin every hour day and night for 21 days. Response was good, but there were temperature rises to as high as 100.6° F. at times. Several abscessed teeth were removed and the usual penicillin routine followed. During and after the treatment, the patient had unexplained paroxysms of hacking, non-productive coughing spells lasting 1 to 2 hours, causing exhaustion. Sodium amytal and morphine had to be used to depress the patient. Bronchoscopy (Dr. S. Salinger) showed marked congestion and edema of the right main bronchus; the left was normal. With symptomatic treatment and frequent psychiatric interviews (Dr. M. Gitelson), the coughing spells lessened and ceased. The patient was discharged on the 63rd hospital day. After being back at work for 6 months, she developed several petechiæ.

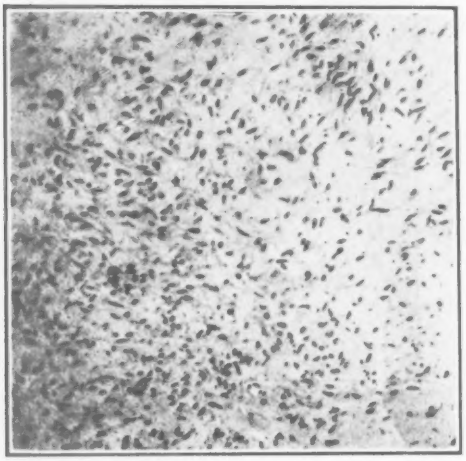

FIG. 11.—Case 9. Early scar tissue. Mitral valve. Iron-hematoxylin-eosin preparation; × 125.

She was readmitted to the hospital where she ran an evening temperature of 99.6° F. Repeated blood cultures have been negative. After several weeks observation she was discharged. Since then she has had occasional petechiæ, but blood cultures are negative. No fever or evidences of heart impairment have been manifest. Thus it appears that the patient has had no recurrences for 13 months.

CASE 12. R. S., a 12 year old boy with a history of "heart murmur" since the age of 2, was admitted on Nov. 20, 1944 with weakness, weight loss, fever, joint pains and frequent epistaxes, of 4 months duration. Examination revealed a temperature of 102.2° F., an enlarged heart, a systolic thrill and a loud rough systolic murmur heard best at the 3rd intercostal space parasternally, a markedly enlarged spleen, numerous petechiæ over the lower abdomen and legs, and early clubbing of the fingers. Blood cultures were positive for *Strep. viridans*, the sensitivity was 0.03 Oxford units. He was treated for 25 days day and night with the hourly intramuscular injection of penicillin varying from 100,000 to 300,000 units daily. Defervescence and clinical improvement were

FIG. 12.—Case 9. Aortic valve. Note the cellular scar tissue covered by regenerated endothelial lining cells. Orcein preparation; × 125.

prompt. There were slight temperature rises following extraction of several infected teeth during the course of therapy. The stay in the hospital otherwise was uneventful. The patient was discharged on the 46th hospital day. The boy is back at school, is asymptomatic and has had no recurrence for 13 months.

CASE 13. (Fig. 3.) S. H., a 38 year old man with a history of congenital heart disease since birth was admitted on Nov. 22, 1944 from another institution where a diagnosis of subacute bacterial endocarditis was made and a total of 5 million units of penicillin given without response. His complaints

were fever, headache and "tightness of the forehead" and generalized malaise of 4 months duration. The diagnosis was confirmed bacteriologically and clinically. On examination, the heart was not enlarged. There was a systolic thrill and loud harsh murmur best heard in the 3rd intercostal space para- and midsternally. There was no sign of *peripheral* embolization nor has any appeared as yet. His stools carried *Ascarsis lumbricoides;* and flagellates were found in the urine; both were successfully treated. The blood cultures were positive for *Strep. viridans,* sensitivity was 0.03 Oxford units. Because of the previous unsuccessful treatment, he was given 300,000 to 500,000 units daily by hourly intramuscular injections day and night. Defervescence was immediate but headaches persisted. One day after completion of the first course of penicillin, the temperature rose and the blood cultures became positive. He was then given a prolonged course of treatment of 92 continuous days of interrupted intramuscular injections using at times concomitantly intravenous drip. The lowest level of penicillin maintained in the blood was 0.16, and often it was 0.50 to 0.74 units per cc. In addition, "booster doses" as recommended by Baehr[1] were given for 15 days. During treatment, there were many episodes of pulmonary embolization. His headaches would disappear for several days and then would reappear. Examination chemically and bacteriologically of the spinal fluid was entirely negative. A neurologic examination was normal. As soon as therapy was again stopped, blood cultures became positive. The organism had not changed its sensitivity. A third course of treatment employing 1.2 to 3 million units daily by continuous intramuscular and intravenous drip was successful. During this last course, he received for 72 hours penicillin dissolved in 3000 cc. of 6% para-aminohippuric acid.[2] His blood penicillin level under this combination rose to 5 Oxford units per cc. This patient has received over 112 million units of penicillin. He is back at work and has had no recurrences for 10 months.

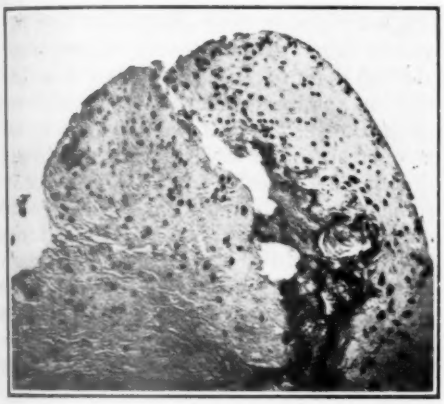

FIG. 13.—Case 9. Mitral valve. Note the area of necrosis. Iron-hematoxylin-eosin preparation; × 125.

FIG. 14.—Case 9. Mural endocardium. Note the plaque indicating healing mural endocarditis. Orcein preparation; × 125.

CASE 14. R. M., a 40 year old man, with a past history of "heart disease" since the age of 20, was admitted on Dec. 10, 1944, from another institution with a diagnosis of subacute bacterial endocarditis of 11 months duration. He had been treated with sulfapyridine, sulfadiazine, and 500,000 units of penicillin before admission. On examination, the patient was obviously very far advanced in his illness. He was dyspneic, orthopneic, had a café-au-lait color with many petechiæ on the soft palate and in both conjunctival sacs, and marked clubbing of the fingers.

The heart was markedly enlarged and there was evidence of aortic and mitral valvular involvement, with gallop rhythm. There was marked edema of the lower half of the body, bilateral pleural effusion and ascites with hepatosplenomegaly. The muscles were obviously wasted and atrophic. The blood cultures were positive for *Strep. viridans*, the sensitivity was 0.08 Oxford units. The temperature was 103° F.; hemoglobin 8 gm., 2.8 million red blood cells. The total blood protein was 4.2 gm. % (2.2 gm. albumin and 2 gm. of globulin). The venous pressure was 20 cm. of water. The circulation time was prolonged. Because of the wasted gluteal muscles and edema, he was given hourly injections of penicillin (12,500 units per dose) day and night into the deltoid muscles. In addition, frequent small whole blood transfusions, digitalis, mercurials, and a high protein (150 gm.) salt free diet were given. The temperature never fell to normal under treatment. By the 15th hospital day the blood albumin level had increased 0.8 gm. %. However, the patient became progressively worse and died in congestive heart failure after receiving a total of 3.9 million units of penicillin for 12 days. The valve lesions are shown in Figures 5 and 6.

The salient autopsy findings (Dr. O. Saphir) were:

1. Subacute bacterial endocarditis (*Strep. viridans*) of the mitral and aortic valves with ulcerations of the aortic cusps and mycotic erosive aneurysm of the mitral valve.

2. Multiple organizing and organized myocardial infarcts (embolic in origin).

3. Marked chronic passive hyperemia of lungs, liver and kidneys.

Case 15. A. B., a 27 year old man, with a past history negative for rheumatic fever was transferred to this hospital on Dec. 28, 1944 from another institution with a diagnosis of subacute bacterial endocarditis. He had been ill for 10 months and had been at several hospitals where he had received various sulfonamides and a total of 3 million units of penicillin irregularly administered. The diagnosis was substantiated clinically and bacteriologically. On examination there were obvious peripheral signs of aortic insufficiency. The heart was markedly enlarged. There was a left hydrothorax, several petechiæ in the right conjunctival sac, and clubbing of the fingers. Blood cultures were positive for *Strep. viridans*, the sensitivity was 0.02 Oxford units. He was given 300,000 to 400,000 units of penicillin by the hourly interrupted or by the continuous intramuscular drip. The temperature never returned to normal and the patient continued to have splenic and renal infarcts. On the 35th day of treatment after he had received 11.4 million units of penicillin, he suddenly became aphasic, lapsed into a coma and died.

The salient autopsy findings (Dr. O. Saphir) were:

1. Subacute bacterial endocarditis of the aortic (*Strep. viridans*) and mitral valves (Fig. 4).

2. Ruptured mycotic aneurysm of the mitral valve.

3. Embolus in the left middle cerebral artery.

4. Hemorrhage in the left cerebral hemisphere.

5. Large septic infarcts of the spleen.

6. Mycotic aneurysm of the splenic artery.

Case 16. E. R., a 21 year old woman had a history of rheumatic pancarditis with congestive failure at the age of 8. Subsequently, she had slight to moderate cardiac disability. She was admitted on Jan. 1, 1945, with fever, painful finger tips of 3 weeks duration, and amenorrhea of 12 weeks duration. Physical examination revealed murmurs of aortic insufficiency and mitral stenosis, Osler nodes on the terminal phalanx of the left ring finger and right first toe and an irregularly enlarged uterus to the size of a 3 months gestation. Friedman test and pregnandiol test for pregnancy were positive. Three successive blood cultures were positive for *Strep. viridans*, the sensitivity was 0.015 Oxford units. She was given 8300 to 16,600 units of penicillin every hour day and night for 56 days intramuscularly. The temperature response was dramatic and the blood stream was easily sterilized. It was felt that continuation of pregnancy was not justifiable because of the previous history of congestive heart failure, and in view of the fact that the patient continued to have frequent small emboli and petechiæ. On the 41st day of treatment, a hysterectomy was performed (Dr. W. Rubovitz), because of numerous moderately sized fibroids. The cord blood was sterile and penicillin was present in about one-half the concentration of the mother's blood, showing that the penicillin passes through the placenta, as has already been reported by Greene and Hobby.[9] During the postoperative course, the patient continued to show several small petechiæ

but otherwise she was well. Therapy was stopped 15 days postoperatively. Blood cultures remained sterile and except for small petetchiæ which have continued to appear since the completion of therapy, the patient has been well. She was discharged on the 75th hospital day and since has been doing light housework. There has been no recurrence for 12 months.

Case 17. M. B., a 15 year old female with a history of chorea in 1938, was admitted on Feb. 20, 1945, with the complaints of fever and weakness of 8 weeks duration and pain in the plantar surface of the left foot of 3 days duration. On examination, there were several conjunctival petechiæ, a fading Osler node on the plantar surface of the first toe of the left foot, a markedly enlarged heart with an early high pitched diastolic murmur at the base and a presystolic crescendo murmur at the apex, and an enlarged spleen. The temperature was 102° F. Several blood cultures were positive for *Strep. viridans*, sensitivity to penicillin was 0.06 Oxford units. This was kindly determined by Dr. L. Loewe of Brooklyn Jewish Hospital, New York. The patient was given 8300 to 10,000 units of penicillin intramuscularly every hour day and night for 8 days with little clinical improvement. The dosage was then increased to 16,666 units intramuscularly every hour for another 6 days. Because of the relative resistance of the organism, 500,000 units per day were administered daily by the hourly intramuscular route for the next 41 days and 1 to 2 million units of penicillin daily by continuous intramuscular drip for 3 weeks. She was discharged on the 135th hospital day. There has been no recurrence for 8 months. However, the patient has had evidence of congestive heart failure and several pulmonary emboli. She has been bedridden for the last 3 months and auricular fibrillation has appeared.

Discussion. 1. *Efficacy of Penicillin Therapy.* Our series to date consists of 17 patients of whom 14 have fully recovered from their infection. All of them have been free from recurrences as of March 1, 1946 (Table 1), the longest follow-up being 20 months, the shortest 8 months. The patients have been closely followed after release from the hospital and all are afebrile, and their blood cultures remain negative. Their red blood count has returned to normal, the leukocytosis has disappeared, and the sedimentation rate has fallen. Some have returned to their former occupation or to school. Of the remaining 3, 2 died during treatment, 1 discharged as a treatment failure died at home. One of the recovered patients died of congestive heart failure 8 months later and several others are suffering from this complication. It has been our experience as well as that of others[4,16] that when the case has been adequately treated and has been "arrested" for a months, relapses have not as yet been observed.

The series is too small to be handled statistically but the results are in accord with those reported by others.[1,3,4,16,18] This is particularly significant since the cases in this study were successive and unselected. There can thus be no doubt that penicillin offers a definite therapeutic approach to what has hitherto been almost invariably a fatal disease.

To obtain the best results, a proper method of penicillin therapy must be established and the factors which may reasonably be expected to influence the outcome should be defined. Some clues in regard to this have been obtained from our study and they will be briefly discussed. As experience grows, these factors undoubtedly will be subject to re-evaluation.

2. *General Condition of Patient.* This does not appear to play any definite part in his recovery. Thus 1 case (Case 14) with wasted atrophic muscles, abnormally low plasma proteins and anasarca—part of which was due to the low osmotic pressure of the plasma proteins—died on the thirteenth day of treatment. Another (Case 13) who was in excellent general condition required 112 million units of penicillin and several months of hospitalization before he responded to therapy. On the other hand Case 10, who was in poor general condition, made a speedy and uneventful recovery.

3. *Probable Duration of Infection.* In a disease like subacute bacterial endocarditis it is often difficult to state with exactness the day of onset. In 3 patients however,

the beginning of the disease followed immediately after teeth extraction. Prophylactic chemotherapy had not been given in these cases. The majority of our patients were ill from 4 to 16 weeks. The 2 who died during penicillin therapy (Cases 14 and 15) were ill for 44 and 40 weeks respectively before treatment was begun by us. Both had entered the ulcerative phase of the disease. It is our impression that the duration of the infection will not of itself alter the outcome of therapy providing complications such as ulcerations, perforations, mycotic aneurysm formation and congestive heart failure have not occurred. The chance of such complications occurring is greater of course the longer the disease continues.

4. *Nature of the Primary Disease.* Ten patients had rheumatic valvular disease, 4 had congenital heart disease (clinically diagnosed as a patent interventricular septal defect), 1 had combined congenital (a patent ductus arteriosus) and rheumatic heart disease, 1 had syphilis, and 1 had no apparent heart disease but a loud systolic murmur was present at the apex on admission. One of the cases with congenital heart disease and a complete heart block showed a prompt response after only 18 days of penicillin treatment. On the other hand, another case (Case 13) with the same congenital defect completed 145 days of treatment before it was successful. In the rheumatic valvular group, there was no correlation between valvular distribution and the effectiveness of therapy. Both fatal cases had combined mitral and aortic disease. The cases with aortic regurgitation however, which recovered from the infection were the ones which developed congestive failure readily.

5. *Resistance of Organism to Penicillin in vitro.* The susceptibility of the organism to penicillin is one of the most important factors in determining the outcome of therapy. In determining the sensitivities of the isolated strains of streptococci from blood cultures, various adaptations of the Oxford cup test[7] and serial dilution method[5] were tried to determine the quickest way of obtaining clinically significant results with a minimum of the common sources of error. The one finally adopted was the serial dilution method. A control was made in each case with a standard strain of *Staphylococcus aureus* of a known sensitivity (Merck, *Staph. aureus* H MB109).

A concurrently run Oxford cup test sensitivity on several isolated strains correlated closely with the serial dilution method finding. The former method was found more practical in several cases where the strain was slow growing (48 to 72 hours). Sensitivities ranged from 0.015 to 0.08 Oxford units for bacteriostasis.

All the cases with strains of streptococci sensitive to less than 0.06 Oxford units responded to penicillin except 1. Case 15, with a sensitivity of 0.02 Oxford units died of a cerebral embolus during treatment. The therapy failures included Case 6 with a sensitivity of 0.06 Oxford units and Case 14 with a sensitivity of 0.08 Oxford units (died during therapy). It is safe to state that as a rule the more susceptible the organism is to *in vitro* penicillin action, the more prompt will be the response to therapy, barring complications. Exceptions, however, do occur. Above a certain *in vitro* penicillin sensitivity (over 0.06 Oxford units in our laboratory*) the cases respond with difficulty.

6. *Method of Administering Penicillin; Route, Dosage, and Duration of Therapy.* We have employed the following methods of administration of penicillin, *viz.*: (1) continuous intravenous or intramuscular drip, and (2) intermittent intramuscular injections.†

It was soon apparent that the use of a continuous drip method required constant attention day and night if the penicillin blood level was to be maintained uniformly high throughout the course of therapy. It has been shown[21] that penicillin is quickly excreted. Like others therefore we have found‡ that the blood level will quickly fall when the injection is stopped

* Our values run lower than determinations by Dr. Loewe's laboratory.

† In 2 patients intermittent "booster doses" as recommended by Baehr[1] were used.

‡ We employed a slight modification of the serial dilution method.

or the rate of administratino decreased. Some patients cannot tolerate the continuous presence of a needle for days on end. In the case of the intravenous route a further disadvantage is that thrombophlebitis occurs and consequently all accessible veins may be eliminated. For this reason, and because less attention is required, we prefer the intramuscular to the intravenous route when a continuous drip is decided upon. Moreover, the blood levels maintained with the former are as high or even higher than with the latter.

In the case of intermittent intramuscular injections, the frequency of the injections should be such that the fluctuations of the blood level are slight. We have found, in confirmation of others,[6,21] that there is little penicillin remaining in the blood serum 60 to 75 minutes after a single intramuscular injection and practically none at the end of 2 hours. The exact concentration varies, of course, with the amount injected and the rate of renal excretion. Fleming[6] has shown that smaller doses given at more frequent intervals will maintain bacteriostasis in the blood for a longer period with the same total dosage than larger doses administered less frequently. Thus, intermittent injections at intervals of 3 or 4 hours are considered unsatisfactory when treating subacute bacterial endocarditis. Therefore, we have employed intermittent intramuscular injections *every hour on the hour day and night for the entire period of treatment.* This will maintain a high effective concentration at all times as we have verified by blood level determinations. We believe this is a satisfactory method and recommend it for future use. The total 24 hour dose is divided into 24 equal parts, each dissolved in 1 cc. of sterile physiologic saline and injected into the gluteal region. At first this may appear to be trying for the patient but within 1 or 2 days they become accustomed to the regimen and are no longer "needle conscious." While the fluctuations in penicillin concentration with this hourly method are greater than with the continuous drip method, the differences are not excessive. With the higher daily dosages of penicillin (one million units or more) the continuous drip method is less wasteful of penicillin.

In 11 cases the hourly intramuscular injection schedule was employed. In the remaining cases interrupted intramuscular injection was combined alternately with continuous intravenous or intramuscular drip.

We agree with Loewe,[16] that the best results are obtained when penicillin blood serum levels are maintained between 5 and 10 times the *in vitro* sensitivity figure. Such high levels are also desirable since there must be penetration of the vegetations and destruction of the organisms there located. The figures in our cases, given in Table 1, represent the lowest level of penicillin concentration in the serum during the 24 hour period when the hourly intramuscular injections were employed. These were obtained in all instances 55 minutes after the last hourly injection. During the first half hour after the injection the serum contained 4 to 10 times this minimal level. Even these levels are not always bactericidal for some strains of *Strep. viridans* but they are bacteriostatic. Thus, early during treatment we were able to obtain positive blood cultures in several cases when the anti-penicillin agent Clarase was added to the culture media.

The usual daily dosage was 200,000 to 300,000 units. At present we are giving larger daily doses to the more resistant cases (1 to 3 million units). The total amount of penicillin given ranged from 3.6 million units for the shortest treated case and 112 million units for the case requiring 145 days of treatment.

The usual course was planned for 21 days. The shortest successful treatment period was 18 days, the longest 145 days. Cases 3, 8, 10, 11 and 12 only required from 18 to 25 days of treatment with uniform success. On the other hand Case 6 was a treatment failure after 158 days of therapy.

The usual planned 3 week course of therapy was continued and the daily dosage increased when the clinical or bac-

teriologic response was unsatisfactory or when embolization, even though sterile, continued. The penicillin was stopped when blood cultures were consistently negative, when the general condition was greatly improved and when signs of active infection were no longer present as indicated by the white blood count, the sedimentation rate and the temperature curve. In 5 cases a slightly accelerated sedimentation rate (Wintrobe and micro-methods) persisted as the only abnormality for several weeks after therapy was completed, but in each instance it eventually returned to normal. If the organism is susceptible to the action of penicillin although more resistant than usual, *viz.*, 0.06 Oxford units or more, we believe that treatment should be made continuous without interruption for longer than 3 weeks and larger daily dosages of penicillin should be used.

After therapy was stopped the patients were observed in the hospital, usually for about a fortnight with frequent blood cultures and other pertinent laboratory procedures before being discharged.

7. *General Measures Used to Supplement Penicillin Therapy.* All patients were placed on a palatable, high caloric, high vitamin diet (but no vitamins were added). The teeth were examined and cared for, and when indicated extractions were done, employing penicillin (5000 units per cc.) soaked sponges to pack the sockets. No untoward results followed the dental care. All cases received two or more transfusions of packed red cells at the beginning of treatment and iron therapy was used continuously in all cases. Bed rest was maintained at first, but as soon as feasible the patients were permitted increasing ambulatory privileges in the hospital.

8. *Response to Treatment and Complications During Treatment.* The rectal temperature curves of most of the cases fell precipitously to normal limits within 24 to 48 hours after penicillin was started with only an occasional slight evening rise to 100.4° F. during treatment, except when complications were present. The fall in temperature was associated with a feeling of "well being" and an increased appetite, and a gradual disappearance of the café-au-lait color. The changes in the patients' personalities were striking; usually after 1 week a negativistic personality was replaced by a normal social temperament. The temperature curves of the fatal cases never reached normal during the treatment period. Some cases (Cases 1, 7 and 9) had a return to normal temperature by lysis. The temperature curve of Case 13 fell to normal during treatment, but immediately rose when the first and second courses were completed. The temperature curve of Case 6 fell to normal by crisis during some courses of therapy, but in others it remained elevated.

Anemia of varying degrees was present in practically all of the cases on admission to the hospital. As the infection was brought under control the red cell count and hemoglobin rose to normal levels.

Some of the complications encountered were incidental or coincidental to the endocarditis. Only one was directly attributable to the penicillin. This reaction consisted of a mild generalized urticaria responding to symptomatic treatment and did not interfere with the penicillin treatment. It occurred in Case 3, a child with hay fever and other allergic idiosyncrasies. It was the only untoward penicillin reaction found in our 17 cases, although we have given as much as 3 million units per day—this is certainly a tribute to the skill in preparing a highly purified penicillin.

One patient (Case 5) developed infectious mononucleosis on the 17th day of treatment. Still another (Case 8) was found to be a carrier of *E. histolytica.* Another (Case 13) was a carrier of *A. lumbricoides* and also had flagellates in his urine. Another patient (Case 9) had a positive Wassermann, Kahn and Eagle serologic tests before and after treatment which was shown at necropsy to be associated with syphilitic aortitis.

One patient (Case 16) was in the fourth month of pregnancy when admitted for treatment. After 6 weeks of penicillin therapy an abdominal hysterectomy was

advised because of a past history of several attacks of congestive heart failure. Her course following operation was uneventful except that after penicillin therapy was stopped she developed two petechiæ. She was afebrile, bacteria-free and asymptomatic, however, and has since remained well.

One other patient had an embolus to the posterior tibial artery after treatment was stopped, from which he quickly recovered. This was non-infected because repeated blood cultures at the time were negative and no signs of infection were present. It appears that during healing of the vegetations and after the vegetations are bacteria free, petechiæ and other embolic manifestations may occur. Petechiæ may reappear in some cases for months.

In 1 case (Case 15), an embolus to the left middle cerebral artery led to a massive cerebral hemorrhage on the 34th day of treatment after 11.4 million units of penicillin had been given. At necropsy friable vegetations (Fig. 4) were present on the right and non-coronary cusps of the aortic valve, from which *Strep. viridans* was obtained on culture; those present on the left cusp and chordæ tendinæ of the aortic leaflet of the mitral valve were fibrotic and calcified; perforation of this leaflet was also present. A mycotic aneurysm of the splenic artery and a large splenic "abscess" due to autolysis of septic infarcts were unexpected findings. *Strep. viridans* was cultured from the septic infarct.

The other fatal case (Case 14) died of congestive heart failure on the 13th day of treatment. His illness was of about 44 weeks duration and he had had congestive heart failure for some time as well as a long standing hypoproteinemia. Examination postmortem revealed ulceration and perforation of a bicuspid aortic valve (Fig. 5), and a mycotic erosive aneurysm of the anterior mitral leaflet (Fig. 6). Culture of the aortic valve revealed *Strep. viridans*. The vegetations on the aortci cusps were large and friable and showed little or no organization on histologic study, whereas those on the mitral valve were small and firm and revealed moderate fibrosis. A right hydrothorax, ascites, chronic passive congestion of the viscera and septic myocardial infarcts were also present.

Case 6 had septic lung infarcts with empyema, *Bact. funduliformis* septicemia and also a relative renal insufficiency, all of which developed under treatment.

In several cases, especially these with aortic regurgitation, congestive heart failure developed when the patients became ambulatory. Three factors are probably involved: (1) the augmentation of the amount of regurgitation as the vegetations were healed, (2) the encroachment on the cardiac reserve as the patients became ambulatory, and (3) the myocarditis and myocardial fibrosis consequent to the infection. The failure has been progressive in some cases; it has required digitalis and mercurial diuretics. One patient (Case 17) has become bedridden on this account, and another (Case 9) died with it.

9. *The Rôle of Heparin.* Although our series is small, the results are as favorable as those reported on the combined use of heparin and penicillin.[4,16] No one has actually proved the need of combining heparin with penicillin, nor have the theoretical considerations for its use been experimentally or clinically demonstrated. The view that it prevents further deposits of thrombotic material on the vegetations, or eliminates vegetations and thus facilitates healing directly, or that it facilitates penetration of penicillin or other chemotherapeutic agents into the vegetations is questioned (*cf.* 11). Embolization is not lessened by its use. In fact experience points to the contrary. More embolic deaths appear to have occurred in the presence of heparin when given intravenously than in its absence (*cf.* 11). It has not been demonstrated clinically that heparin acts in a synergistic manner with penicillin.

While final judgment must still be deferred, we do not at present recommend the use of an anti-coagulant because:

(*a*) The results with penicillin alone appear to be as favorable as those with penicillin plus heparin.

(*b*) The cost of therapy is increased by the use of heparin and its proper administration requires a more elaborate organization.

(*c*) Heparin often causes febrile reactions which obscure and confuse the clinical picture.

(*d*) Local pain is common following the subcutaneous administration of heparin.

(*e*) The intravenous use of heparin is hazardous (*cf.* 11).

Future efforts should be diverted in other directions, specifically in solving the problem of the cure of cases with strains of *Strep. viridans* which are more resistant than those usually encountered.

10. *Necropsy Evidence of Healing.* The findings in Case 9 are significant in provgin by necropsy check that healing of subacute bacterial endocarditis is produced by effective penicillin therapy.

Summary and Conclusions. 1. Seventeen *successive, unselected* cases of bacterial endocarditis have been treated with penicillin alone. Fourteen cases have "recovered," the longest follow-up being 20 months, the shortest 8 months as of March 1, 1946. Two cases have died during treatment and 1 case sent home as a treatment failure died at home. The autopsied cases showed infected vegetations at necropsy. One of the "recovered" cases developed progressive congestive heart failure, and died 8 months after "recovery." At necropsy a healing and healed endocarditis was found.

2. Eleven cases were treated exclusively by intramuscular injections of penicillin every hour day and night for 3 to 4 weeks using 200,000 to 300,000 units daily. We recommend this method for the average case since it maintains an adequate bacteriostatic penicillin level and it is *effective.* In the remaining cases, interrupted intramuscular injection was combined alternatively with continuous intravenous or intramuscular drip.

3. Cases with more resistant organisms (sensitivity 0.06 Oxford units or greater as determined in our laboratory) should receive larger daily dosages over longer periods of time.

4. Heparin was not employed in any ease; we do not at present recommend its use.

5. Penicillin alone is an effective agent in the treatment of subacute bacterial endocarditis.

We wish to thank Drs. E. Davis, R. Herzog, M. Lev, J. Meyer, P. Rosenblum and S. O. Schwartz for referring private patients to us. The bacteriologic and hematologic studies were carried out with the technical help of Miss H. MacLean, A.B., and Mrs. R. Herzog, respectively.

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OBSERVATIONS ON THE TREATMENT OF SCARLET FEVER WITH PENICILLIN

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IN the treatment of hemolytic streptococcal infections of the throat, it is desirable to obtain not only a clinical cure, but also to eliminate the organisms from the patient's nose and throat to prevent the establishment of a convalescent carrier state. This is especially true in military populations and wherever there is a rapid turnover of personnel. Many workers have demonstrated the failure of sulfonamides, either in therapeutic or prophylactic doses to prevent or cure the "Strep. carrier."[1,3,5,7] Recently, however, reports[2,4] have commented on the efficacy of penicillin therapy in the treatment of streptococcal pharyngitis and scarlet fever, and Plummer[6] has reported a small series of patients with streptococcal pharyngitis and tonsillitis treated with varying doses of penicillin. He was able to demonstrate that recurrent positive throat cultures developed in 8 of 9 patients treated with 100,000 to 150,000 units over a 1-day period; in 4 of 9 patients treated with 240,000 units over 3 days; and in but 1 of 10 patients treated with 540,000 units over a 6-day period.

It was believed to be of value to determine not only the minimal effective dosage of penicillin in the treatment of scarlet fever, but also that necessary for the elimination of the convalescent carrier phase. A total of 118 patients were available for this study over the period of February to June 1945.

All patients in the series were enlisted Naval personnel, young and in good health. A diagnosis of scarlet fever was based on the clinical picture of pharyngitis, fever and a typical rash; and in 76% of the cases, the initial throat culture was positive for beta hemolytic streptococci. The plan of therapy utilized 3 dosage schedules of penicillin as follows:

1. Total dosage 240,000 units: 10,000 units every 3 hours, or 80,000 units per day for 3 days.

2. Total dosage 360,000 units: 10,000 units every 3 hours or 80,000 units per day for 3 days; then 10,000 units every 6 hours or 40,000 units per day for 3 days.

3. Total dosage 480,000 units: 10,000 units every 3 hours or 80,000 units per day for 4 days; then 10,000 units every 6 hours or 40,000 units per day for 4 days.

Patients were housed in covered cubicles containing 5 patients each, under isolation and with minimal outside contacts. Throat cultures were taken on the day of admission and every 2 to 3 days for the duration of their stay in the hospital, which was 14 to 21 days. The post therapy follow up varied from 2 days to 2 weeks, and all patients were kept on isolation during the period. Penicillin (Eli Lilly) was the preparation used.

Results. The results were judged by: (*a*) the clinical response to therapy; (*b*) the percentage of complications after therapy; (*c*) the development of positive throat cultures following each of the 3 dosage schedules.

Clinical Response to Therapy. All cases treated with penicillin showed a good clinical response, in that the temperature dropped to normal and there was marked symptomatic improvement in 24 to 48 hours. Although several cases showed a

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† This article has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the U. S. Navy. The opinions and views set forth in this article are those of the writer and are not to be considered as reflecting the policies of the Navy Department.

few residual organisms on the second day of therapy, all but 1 of the 118 cases had a negative throat culture during the course of penicillin therapy, regardless of the total dosage. Complications did not develop in any case during the therapy.

Incidence of Complications. Any rise in temperature (after completion of therapy) accompanied by recurrence of rhinitis, otitis media, sinusitis, or adenitis was considered to be a complication. The incidence of complications was highest (31%) in the 240,000 unit series and lowest (6%) in the 480,000 unit series (Table 1). Each one of these complications in a patient was found to be accompanied by a recurrence of a positive throat culture.

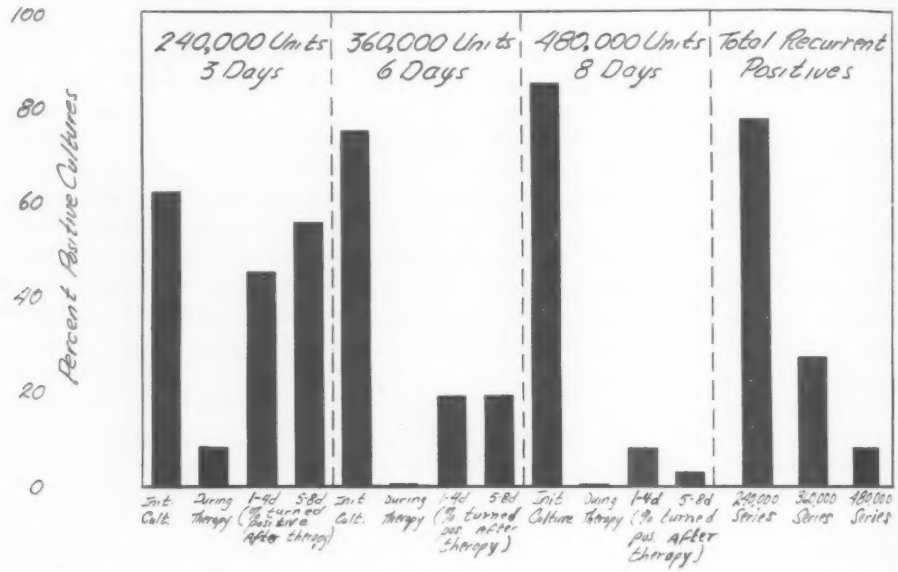

CHART 1.—Recurrence of positive throat cultures after pencillin therapy in scarlet fever.

Effect on Throat Cultures. The effect of varying dosages of penicillin on throat cultures taken after cessation of therapy is shown on Table 2 and Chart 1. The method of analysis described was necessary since the follow-up period on each patient varied and patients with positive cultures and recurrent symptoms were hospitalized and followed for a longer period than those with negative cultures. The follow-up period was divided into 4 day intervals, and among the patients observed through each of these periods, the number of those developing positive throat cultures was determined. It is clear that, in the 480,000 unit series, despite a higher percentage of initial positive cultures, there was a marked reduction in the incidence of recurrent positives after completion of therapy. A group of 12 of these patients was followed for a 2 week convalescent period of hospitalization, and cultures taken over this period showed that all throats remained negative for beta hemolytic streptococci for the entire time. The overall incidence of recurrent positive throat cultures (Tables 2 and 3) demonstrates clearly the effectiveness of the 480,000 unit dosage scheduled in the maintenance of negative throat cultures in convalescent patients. Those turning positive were but mildly ill, *i. e.*, carriers only.

*Typing and Sulfonamide Resistance Studies.** Typings were obtained on 57 of

* Streptococcal typings and resistance studies were kindly done by Lt. Comdr. Armine Wilson, (MC) USNR, Streptococcal Typing Laboratory, National Naval Medical Center, Bethesda, Md.

the 90 initial positive throat cultures and of this group, 25 were tested for sulfonamide resistance. The results of these studies are shown in Table 4. If these typings can be considered representative of the entire series, about 60% of the infections in this series were due to Type "A" Group 17, and 28% were due to Type "A" Group 19. Together, these two types were isolated from 89% of the cases.

Sulfonamide resistance studies on these strains revealed that 17 out of the 18, or 95% of the Type 17 organisms were resistant to sulfonamides in a concentration of 25 mg. per 100 cc.. Of all the organisms tested, 72% showed sulfonamide resistance. This high incidence of sulfa-resistant strains of organisms well emphasizes the need of penicillin therapy in treatment of patients with streptococcal disease.

In 9 instances it was possible to obtain typings of the initial positive culture and of recurrent positive cultures. These results are shown in Table 5. In 8 out of

TABLE 1.—INCIDENCE OF COMPLICATIONS

Dosage series	No. cases	Recurrent symptoms	% complication
240,000 un., 3 days	26	8	31
360,000 un., 6 days	44	6	14
480,000 un., 8 days	48	3	6

TABLE 2.—RECURRENCE OF POSITIVE THROAT CULTURES AFTER PENICILLIN THERAPY (OVER 4 DAY FOLLOW-UP PERIODS)

		1–4 days		5–8 days		9–12 days		12 days +	
Dosage series	% pos. at onset	Cases observed	% pos.*	Cases observed	% pos.*	Cases observed	% pos.*	Cases observed	% pos.*
240,000 un., 3 days	62	21	45	15	53	2	100	—	—
360,000 un., 6 days	75	43	19	21	19	2	0	1	0
480,000 un., 8 days	85	39	8	28	4	10	0	12	0

* % turned positive during each 4 day follow up period.

TABLE 3.—OVERALL RECURRENCE OF POSITIVE THROAT CULTURES AFTER PENICILLIN THERAPY

Dosage series	Cases	% positive at onset	% positive after therapy
240,000 un., 3 days	26	62	77
360,000 un., 6 days	44	75	27
480,000 un., 8 days	48	85	8

TABLE 4.—TYPING AND SULFONAMIDE RESISTANCE STUDIES

Type	Not sulfa-resistant	Resistant (to 25 mg. Per 100 cc.)	% sulfa-resistant	Resistance not determined	Total typed	% of total cases
A-17	1	17	95	17	35	61
A-19	2	1	33	13	16	28
A-30	3	0	0	1	4	7
Others	1	0	0	1	2	4
Total	7	18	72	42	57	100

TABLE 5.—COMPARISON OF STREPTOCOCCAL TYPES ISOLATED FROM INITIAL THROAT CULTURES WITH THOSE ISOLATED FROM RECURRENT POSITIVE THROAT CULTURES

Series	Case No.	Initial type	Recurrent type
240,000 un., 3 days	I–3	A-17	A-17
	I–8	A-17	A-17
	I–9	A-17	A-17
360,000 un., 6 days	II–2	A-17	A-17
	II–3	A-17	A-17
	II–31	A-17	A-17
	II–12	A-30	A-30
480,000 un., 8 days	III–1	A-17	A-17
	III–2	A-17	A- 6

9 instances, the recurrent type was the same as the initial type. In 1 instance, Case No. 2 in the 480,000 unit series, the recurrent type was different from the initial type, indicating a new infection. In the other instances, because of high incidence of Type 17 in this series, it could not be determined whether results represented a new infection or a recurrence.

An attempt was made by *in vitro* studies to determine the possibility of penicillin resistant strains of streptococci in some of the patients in the series, but no evidence for such could be found.

Discussion. With the development of strains of streptococci resistant to the action of sulfonamides, 2 problems arose in the treatment of scarlet fever: (1) the clinical response to sulfonamides was delayed or absent, and (2) throat cultures remained positive for beta hemolytic streptococci, despite sulfa therapy. These convalescent carriers were disseminating virulent organisms back into their environment, thus acting as foci for the spread of further streptococcal disease. The sensitivity of the streptococcus to penicillin made the drug an ideal agent for the treatment of streptococcal disease and for the elimination of the organisms from the throats of convalescent patients. In the control of respiratory disease in groups of men, it is this latter problem, the elimination of the convalescent carrier phase, that becomes especially important. There are perhaps other and possibly more effective ways of using penicillin for this purpose. This study, however, represents our past experience in the search for an optimal dosage schedule.

Summary and Conclusions. 1. Three series of scarlet fever patients were treated with increasing dosages of penicillin: 240,000 units over a 3 day period; 360,000 units over a 6 day period; and 480,000 units over an 8 day period.

2. The clinical response to penicillin was good in all cases.

3. The incidence of complications was highest (31%) in the 240,000 unit series, and lowest (6%) in the 480,000 unit series.

4. The rate of recurrence of positive throat cultures was highest (77%) in the 240,000 unit series, and lowest (8%) in the 480,000 unit series.

5. Of the organisms found, 89% were Types A–17 and A–19. Of the organisms typed, 72% were resistant to sulfonamides in concentration of 25 mg. per 100 cc. or more.

6. The use of 480,000 units of penicillin over an 8 day period is a satisfactory method for the treatment of scarlet fever, and for preventing the establishment of a beta hemolytic streptococcus carrier state in the convalescent patients.

NOTE: During the month of September, 1945, 12 patients with scarlet fever were treated with 480,000 units of penicillin over a 3 day period (20,000 units every 3 hours for 3 days). In this group, throat cultures on all patients were positive for beta hemolytic streptococci at the onset and became negative during therapy. Recurrent positive throat cultures were obtained on 11 patients within 8 days following the cessation of therapy. Of these patients, 6 required a second course of penicillin therapy because of recurrence of clinical symptoms. These data suggest that in the treatment of streptococcal infection with penicillin, the duration of therapy is as important as the total dosage of penicillin used.

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SLOWLY PROGRESSIVE OCCLUSIVE THROMBOSIS OF THE ABDOMINAL PORTION OF THE AORTA

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Occlusion of the abdominal portion of the aorta may occur by emboli lodging at the bifurcation of the aorta, by acute or rapidly progressive thrombosis, by thrombi developing on emboli and by chronic or slowly progressive thrombosis. The symptomatology presented by these entities varies according to the rate of development and extent of the lesion: those associated with rapidly progressive occlusion present a relatively clear cut diagnostic clinical picture; but the clinical findings of the slowly progressive occlusion are insidious and easily overlooked. Three cases in the latter group are presented with emphasis on the clinical recognition of the condition.

Clinical Abstracts. Case 1. S. S., a 52 year old white woman, had multiple hospital admissions and visits to the Out-Patient Department of the St. Luke's Hospital for unrelated conditions. Fortunately, through contacts by multiple hospital admissions and visits to the Out-Patient Department, a fairly detailed record of the patient had been maintained. On Jan. 13, 1938, fixed parametrial tissue, a mass in the cul-de-sac, and a bloody vaginal discharge were found and a clinical diagnosis of "carcinoma of the cervix, stage four" was made. No biopsy was taken. The patient was referred to the Roentgenologist for deep therapy. She received 2450 "R" units from Jan. 19 to March 1, 1938. No radium was inserted. The blood pressure, frequently recorded, was never higher than 130/90 mm. Hg. Eighteen days after the last Roentgen ray treatment there developed pain in the left leg and black discoloration of the third toe of the right foot. It was then revealed, for the past several years she had suffered with varicose veins in both legs and had experienced severe pain on walking. Pressure over the tibias and calf muscles also elicited moderate pain. Her blood pressure was 135/88. With the diagnosis of peripheral arteriosclerotic disease she was given daily Pavex treatments to both feet without appreciable benefit.

In the following 2 months the gangrene extended slightly, both feet became slightly cyanotic and cold, the right somewhat worse than the left, and no pulse could be felt in either foot. Blood pressure on May 18, 1938 was recorded at 164/92. Because of severe pain as well as the gangrene the right lower extremity was amputated through the middle of the leg. Examination of this specimen showed no arteriosclerosis. The operative stump became gangrenous necessitating reamputation through the middle of the thigh 1 month later. This specimen revealed old thrombosis of the femoral artery and recent thrombosis of other arteries and veins.

In August, 1939 she reappeared complaining of pain in the right parietal region of her head, dizziness and occasional vomiting for the past $3\frac{1}{2}$ months. At this time her blood pressure was 195/120. The blood vessels in the fundi of her eyes were moderately sclerotic. There was moderate cyanosis. No arterial pulsations could be felt at the knee or ankle of the left lower extremity. Clinical diagnoses of generalized arteriosclerosis, hypertensive cardiovascular disease with possible prodromata of "stroke" and thrombosis of left femoral blood vessels were made. The patient was last admitted on Oct. 5, 1939 for treatment of a chronic cystitis. Following cystoscopy a retroperitoneal pelvic cellulitis developed. The patient died 3 days

later. The highest recorded blood pressure, 250/110, was found on Oct. 14, 1939, the day of her death.

Autopsy. The autopsy revealed an extensive retroperitoneal abscess in the pelvis extending along the left psoas muscle. The origin of the abscess could not be traced. There was a considerable degree of chronic hemorrhagic cystitis and purulent urethritis but no perforation of the wall. No evidence of carcinoma could be seen in the pelvis or genitalia.

The aorta, from the bifurcation to the level of the lower border of the ostium of the celiac artery, was completely occluded by an old thrombus. This portion of the aorta was moderately constricted, measuring only 1.4 cm. in diameter. The wall at this level revealed a moderate degree of arteriosclerosis. The patent portion of the aorta presented only slight atherosclerotic change. The thrombus extended into both common and internal iliac arteries, into the left external iliac artery and the proximal 0.5 cm. of the right external iliac artery. The orifice of the left renal artery was partially obstructed by the aortic thrombus, but the right renal artery was completely occluded in the proximal 1 cm. The inferior mesenteric artery was also completely occluded.

A moderate reduction in size of the right kidney (70 gm.) was attributed to extensive ischemic atrophy. The left kidney presented a severe acute passive congestion and a moderate compensatory hypertrophy (210 gm.). The arterioles of both kidneys were unaltered, but the small and moderate sized arteries revealed a moderate degree of sclerosis. No nephrosclerosis had developed. A few old infarcts were noted in the spleen. The heart weighed 350 gm., indicating only a slight amount of hypertrophy. No abnormality could be seen in the other abdominal viscera or in the lungs or brain.

Though the aortic thrombosis in this case was not the cause of death, the onset of the hypertension is believed to have occurred when the aortic thrombus involved the orifices of the renal arteries. The relation between the two will be discussed below. The death here was due to the extensive retroperitoneal suppurative cellulitis.

Case 2. J. S., a 54 year old white man, was first seen in the diabetic out-patient clinic of the Cedars of Lebanon Hospital in June 1935, with intermittent claudication and paresthesias of both feet and a feeling of great weakness of the legs after moderate exercise. He had been known to have diabetes mellitus for about 2 months. At that time, his blood pressure was 150/90 mm. Hg. Pulsations were noted to be distinctly diminished in the posterior tibial arteries at this time. Treatment was symptomatic.

About 1 year later, he was transferred to the peripheral vascular disease clinic with the same complaints. Thermocouple readings at that time showed a drop in temperature from the mid-portion of both legs to the feet. The large toe and plantar aspect of both feet registered a reading of -2 and $-3.5°$ respectively. The legs were pale and blanched when elevated, becoming slightly cyanotic when dependent. A dorsalis pedis pulse was noted in the right foot but not in the left. No records were made of the other pulses at this time. The patient was treated with hypertonic sodium chloride solutions intravenously but without beneficial effect.

During the following year, it was noted that except for the femorals no pulsations were palpable in either lower extremity and areas of partial anesthesia developed on the lateral aspect of both ankles. No trophic disturbances were seen.

Shortly thereafter he was referred to the cardiac clinic because of angina pectoris and exertional dyspnoea. There he was followed rather closely for the next 2 years. A diagnosis of arteriosclerosis of the coronary arteries with myocardial fibrosis was made, supported by electrocardiographic changes. During this period the blood pressure rose from 140/90 to 190/100 mm. Hg.

In 1942 symptoms of cardiac failure developed and the patient was first admitted to the medical service of the Cedars of Lebanon Hospital in March of the same year. Physical examination revealed moderate peripheral edema and pulmonary edema. Again it was noted that the arterial pulses were absent in both lower extremities. Treatment was symptomatic and recovery excellent so the patient was discharged to a rest home in 1 week.

He was readmitted to the hospital 11 months later with recurrence of his cardiac failure. This time there was auricular fibrillation and response to therapy was slower.

His final admission to the hospital occurred in July of 1943. He had been awakened from a sound sleep by an overpowering

pain in the abdomen which made him feel faint. His wife, terrified by his ashen pallor and listlessness, secured immediate medical aid and he was admitted to the hospital 3 hours later. At that time he was in deep shock. The abdomen was distended with moderate generalized tenderness, but no rigidity could be found. He died 14 hours later, still in profound shock.

Autopsy. Autopsy revealed an extensive hemorrhagic infarction involving practically all of the small intestine and the cecum. The diameter of the lower half of the abdominal portion of the aorta was moderately smaller than that at any point proximal to it. There was a marked ulcerative arteriosclerosis of the aorta, most pronounced, as usual, in the abdominal portion. A large firm thrombus with moderately advanced peripheral organization completely filled the lower half of the abdominal portion of the aorta, obliterating the orifice of the inferior mesenteric artery, extending distally into both common, internal and external iliac arteries and into the proximal portion of the femoral arteries. Proximally, the thrombus completely filled the aorta to a point just below the orifices of the renal arteries. Above this level, the anterior portion of the thrombus extended along the aortic wall between the orifices of both renal arteries, partially occluding that of the left renal artery, to reach the orifice of the superior mesenteric artery which it completely occluded. The proximal 5 cm. of the superior mesenteric artery was filled with a fresh thrombus.

The heart weighed 590 gm. It was moderately hypertrophied and revealed severe coronary arteriosclerosis with atherosclerotic occlusion, an old healed myocardial infarct with aneurysmal dilatation of the ventricular wall, and organizing mural thrombi in both the left ventricle and left atrium.

The spleen and the left kidney presented a few old healed infarcts. Those in the kidney could have resulted from embolic pieces of thrombotic material from the aorta, while those in the spleen would have resulted more likely from the mural thrombus in the heart.

Only a minimal degree of sclerosis of the large intrinsic renal arteries was observed.

The death of this patient was undoubtedly due to a slowly progressive thrombosis of the abdominal portion of the aorta, developing on the severe aortic sclerosis, complicated by a hemorrhagic infarction of the intestinal tract when the thrombus occluded the superior mesenteric artery. Postmortem blood culture revealed a *B. welchii* septicemia. The hypertension could have developed, as in the previous case, at the time of the partial occlusion of one renal artery by the aortic thrombus. The relation between the two will be discussed below.

CASE 3. J. H., a 53 year old white man, was admitted to the Cedars of Lebanon Hospital with dyspnea and orthopnea in October 1942. For a year before admission he had suffered from weakness and exertional dyspnea and occasional dizzy spells. He volunteered no complaints referable to his lower extremities.

His blood pressure was 240/110 mm. Hg on admission. The heart was large and the rhythm regular. The rate was 100 per minute. A systolic murmur could be heard. Fine râles were present throughout both lung fields. No pulses were noted in either lower extremity. The blood Wassermann and Kline tests were positive.

The patient was responding relatively well to therapy for hypertensive cardiac failure when suddenly he had a short generalized convulsion which passed off rapidly. Five minutes later, he had a few more clonic convulsions and died.

Autopsy. At autopsy, marked arteriosclerosis of both the thoracic and abdominal portions of the aorta was present. Many of the arteriosclerotic plaques were ulcerated. The lower two-thirds of the abdominal portion of the aorta and the common iliac arteries were completely occluded by a sandy brown thrombus with peripheral fibrosis. It extended up to the level of the renal arteries partially occluding the orifices of both. There was a small accessory renal artery on the left which was not occluded. The orifice of the superior mesenteric artery was not involved by the thrombus.

The heart weighed 660 gm. It was considerably hypertrophied and repeated section showed no evidence of fibrosis. The coronary arteries revealed only slight sclerosis with slight focal stenosis of their lumina.

The kidneys were of average size and presented moderate arteriolar and arterial nephrosclerosis.

The brain showed considerable sclerosis of the basilar and intrinsic arteries. Their lumina were considerably stenosed but not

thrombosed. Repeated coronal section of the brain revealed small areas of encephalomalacia involving chiefly the basal ganglia and pons.

Examination of the other organs of the body did not add to the evaluation of the case.

The death of this patient was apparently due to cerebral arteriosclerosis with multiple areas of encephalomalacia complicated by hypertensive cardiac failure. As in the first case the aortic thrombosis here did not contribute directly to the death of the patient. Though a moderate degree of arterial nephrosclerosis was present, the encroachment of the aortic thrombus on the orifices of the renal arteries may have a causal relationship to the hypertension as will be discussed below.

Discussion. Occlusion of the lower portion of the abdominal aorta may occur in a variety of ways, the symptomatology being determined essentially by the rate and extent of the process. Emboli, most commonly from endocardial thrombi, lodging at the bifurcation produce the most common type of occlusion with well recognized and dramatic clinical findings. Gangrene usually develops, is bilateral and usually located below the knees.[15] Paresis and anesthesia, due to ischemia of the spinal cord are relatively constant.[20] There are numerous reports on the recognition and successful treatment of this type of aortic occlusion.[1,2,15,20,24]

Acute or rapidly progressive thrombosis of the abdominal portion of the aorta produces essentially the same symptomatology. It may be superimposed on embolism which incompletely occludes the aorta at the bifurcation or the iliac arteries;[20] it may result from infection of the umbilicus in infants with subsequent septic thrombosis of the umbilical and hypogastric arteries;[16,25] it has been reported in luetic aortitis,[8] rheumatic fever and other acute infections.[20] In this type of thrombosis, in addition to the effect on the lower extremities, the rapid progression of the thrombus proximally leads early to infarction of the abdominal viscera and death.

On the other hand, slowly progressive occlusive thrombosis of the abdominal portion of the aorta is uncommon. It is of insidious onset and of long duration, usually a number of years. Due to inadequate differentiation in much of the literature between these types of aortic occlusion, it is difficult to attempt to determine the total number of recorded cases of the chronic form. Some idea of its frequency may be secured from several sources. Among 1500 consecutive autopsies at the Cedars of Lebanon Hospital, only 2 cases were seen. Siegel and Garvin[22] found 9 cases in 6457 autopsies performed at the Cleveland City Hospital. Bull[3] states that he has found 9 cases of complete thrombosis of the abdominal aorta in 6000 autopsies. Lueth reported 1 case in 1047 autopsies at the Research and Educational Hospital.[14] From these figures the mean incidence is approximately 0.12%. Males are more frequently affected than females.

This type of aortic thrombosis is usually a complication or sequela of arteriosclerosis of the aorta as it was in the 2 cases seen at the Cedars of Lebanon Hospital. Its predilection for the abdominal portion of the aorta is probably best explained by the fact that atheromatosis is most advanced in this area and is facilitated to some extent by eddies set up by the division of the current of blood at the bifurcation. The thrombosis probably first occurs in an ulcerated atheromatous plaque, being, in its early stages, mural in nature, and with further superimposed thrombosis, the entire aortic lumen is occluded. A study of this process has been reported by Clark *et al.*[4] Sauer[21] believes that occasionally recovery may occur from the immediate effects of embolism of the aortic bifurcation and that the picture of chronic occlusive thrombosis then may be superimposed. He is supported in this contention by 2 other cases,[6,20] but this mechanism is distinctly infrequent. In the first case described by us, though it cannot be proved, there is a strong possibility that the thrombosis was initiated

by the Roentgen radiation, probably assisted by the retroperitoneal inflammation since neither of these processes alone are known to thrombose large arteries. This mechanism for the production of aortic thrombosis is undoubtedly rare. In almost all reported cases, including ours, the thrombosis extended into both common iliac arteries, the internal and external iliac arteries and at times into the femoral arteries. Proximally the thrombus has been found as high as the level of the ostium of the superior mesenteric artery.

The early symptoms of this occlusion of the aorta result from the inadequate blood supply to the lower extremities, to the lumbar portion of the spinal cord and possibly to the pelvic organs. Many of these clinical findings are among those commonly complained of by elderly people and unless aortic thrombosis is suspected it is apt to pass unrecognized. Many of these patients, including those reported here, complained of disturbances in the lower extremities commonly associated with peripheral arterial disease, such as intermittent claudication, coldness of the feet, and cyanosis of the feet on exercise. An important clinical clue in favor of the thrombosis of the aorta, however, lay in the fact that the popliteal and posterior tibial arterial pulses were completely absent bilaterally. In peripheral vascular disease such equality may occur but is not ordinarily seen. In some of these cases, and in 1 of ours (J. S.), femoral arterial pulses were recorded, but which in retrospect probably were transmitted impulses from the aorta. Gangrene of the extremities may, but usually does not, result from slowly progressive thrombosis of the aorta because of the time factor which permits the development of collateral circulation. Case 1 of our group which did develop gangrene probably exemplifies the exception, and may have been due to a more rapid progression of the occlusive thrombosis in this case than in the other cases.

Déjérine's syndrome,[23] originally described in luetic arteritis affecting the lumbo-sacral arteries, consists essentially of a paresis of the lower extremities, brought on by exercise and relieved by rest. This syndrome results from inadequate arterial supply to the lower segments of the spinal cord.

Reichert, Rytand, and Bruck[17] have described a similar condition in arteriosclerosis of those blood vessels and have reproduced the syndrome by ligation of either the lumbo-sacral arteries or the abdominal portion of the aorta. It is of interest to note also that when the abdominal portion of the aorta is occluded in dogs, the most troublesome consequence is paresis of the lower extremities, particularly after exercise.[9] Gangrene does not result.

One of the patients (J. S.) presented a story very suggestive of Déjérine's syndrome and it is quite possible that had it been sought in the other cases, a similar history might have been obtained.

LeRiche[13] also described, among more than 20 cases of chronic occlusive thrombosis of the aorta, "extreme fatigability" of the lower extremities, which suggests Déjérine's syndrome. He also reported that he had seen no trophic disturbances. To the symptoms so far described, LeRiche adds impotence as another, which he ascribes to a deficient blood supply to the penis but which, in our opinion, could be due just as likely to the ischemia of the spinal cord or sympathetic nerves controlling erection of the penis.

As long as the aortic thrombus remains below the level of the renal arteries, the disease is only moderately incapacitating and in itself is not a threat to life. Apparently occlusion of the orifice of the inferior mesenteric artery as in our cases and in several of the reported cases[5,14,19] produces no infarction of the intestine. However, as the thrombus extends proximally, it may produce a stenosis or occlusion of the orifices of the renal arteries or of the superior mesenteric artery.

As the thrombus occludes the renal arteries portions of the thrombus may break off and embolize to the kidney,

resulting in infarcts. The presenting symptom in such cases may be hematuria.

This is exemplified in 1 of our cases (No. 2) and in cases described by Siegel and Garvin,[22] Doane and Blumberg[5] and Hamilton.[10] In our cases and in 2 other reports in which partial occlusion of the renal orifice was observed,[12,18] a pronounced hypertension was also present. The cases reported by us presented variable degrees of occlusion of the renal arteries from partial to complete. Case 1 was closely followed and the onset of a progressive hypertension was observed about 1 year prior to death. In this case particularly it appears as though the onset of the hypertension is coincidental with the stenosis of the renal arteries by the thrombus. Case 2, which was uncomplicated by nephrosclerosis also strongly suggests a relationship between the stenosis of the renal artery orifice and the hypertension. In Case 3 the nephrosclerosis alone could have accounted for the hypertension but the rôle of the aortic thrombus occluding the renal artery orifice in causing or contributing to the hypertension cannot be entirely excluded. This partial occlusion of the renal arteries by thrombi, with resultant renal ischemia, are relatively close clinical analogies to the renal ischemia with resultant hypertension produced experimentally in dogs by means of a stenosing clamp on the renal arteries as described by Goldblatt.[7]

As in 1 of our cases (J. S.) and in others culled from the literature,[1,12,24] the thrombus may extend along the aortic wall between the orifices of the renal arteries and may occlude the orifice of the superior mesenteric artery. In such cases, the terminal clinical picture is that of intestinal infarction produced by either thrombosis of the mesenteric artery or embolism by a piece of the aortic thrombus.

The time interval between the onset of the early signs and symptoms of chronic aortic thrombosis and the onset of visceral involvement is usually quite long. In 1 of our cases (J. S.) which is quite representative, this time interval was approximately 5 years.

The only attempt at therapy in chronic occlusive thrombosis of the aorta has been made by LeRiche.[13] In the early stages, when the diagnosis is made, he recommends resection of the thrombosed portion of the aorta and iliac arteries, apparently to prevent proximal extension of the thrombus, and also resection of the first and second lumbar ganglia. He states he has performed either one or both of these procedures in 5 patients, but unfortunately his report is not sufficiently detailed to permit critical evaluation of his results.

Summary and Conclusions. Three cases of slowly progressive occlusive thrombosis of the abdominal portion of the aorta are presented. The disease is usually secondary to a severe ulcerative arteriosclerosis of the arterial wall, but may follow an embolism to the bifurcation of the aorta, or more rarely, thrombosis of the pelvic arteries after irradiation. Its mean autopsy incidence is 0.12%. The characteristics of this syndrome that permit differentiation from other forms of aortic occlusion are: insidious onset; protracted course; usually, but not always, absence of gangrene; absence of pulses in both lower extremities; weakness in legs after exercise with recovery on rest; and the appearance of arterial hypertension or of signs of visceral infarction years after the signs of muscular insufficiency in the lower extremities were first experienced.

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IMPORTANCE OF URINARY CHLORIDE DETERMINATIONS IN TREATMENT OF PATIENTS HAVING PYLORIC OBSTRUCTION*

A Review of 50 Cases of Duodenal Ulcer

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The importance of fluid and mineral salt balance in patients having gastric retention due to duodenal ulcer is well recognized. However, the need for administering sodium chloride is commonly based on plasma chloride determinations. Haden[6,7] pointed out that the plasma chloride content is preserved at the expense of the tissue chloride so that the amount of chloride in the blood may be normal when the tissue chlorides are depleted. Therefore, the true status of chloride deficiency would not be indicated by plasma chloride alone.

As a result of Haden and Orr's[8] experimental work 20 years ago, urinary chloride determinations have been used routinely at this clinic with gratifying results as a basis for the sodium chloride needs of patients. The purpose of this review is to present further evidence, derived especially from study of 50 patients with duodenal ulcer, that urinary chloride determinations furnish more accurate indications for sodium chloride therapy than do plasma chloride determinations. Twenty patients did not have true pyloric obstruction due to cicatricial narrowing, since the obstruction was relieved by medical management. The remaining 30 patients were operated upon.

The shortest period of medical management was 3 days, the longest 9 days, and the average 5 days. The details were similar to those reported by Collins and Rossmiller.[2] In addition to restoring fluid and electrolyte balance, either single nightly gastric aspiration or Wangensteen drainage during part of each 24-hour period was included. Fluid and sodium chloride balance was not considered to be present until the patient was excreting in a 24-hour period at least 1500 cc. of urine having a normal specific gravity and containing at least 5 gm. of sodium chloride. Operation was not undertaken until these conditions were established.

Methods. *Plasma Chlorides.* The Osterberg modification of the Whitehorn method[12] was used for determination of plasma chlorides. We consider that the normal values for this method are 520 to 595 mg. per 100 ml.

Urinary Chlorides. The Volhard-Hardy procedure[10] was used for the determination of urinary chlorides. Chloride values in the urine are measured in terms of sodium chloride. The normal 24-hour urinary chloride excretion value is 5 to 10 gm.

When the usual laboratory facilities are not available, urinary chloride determinations are easily made using the simple procedure described by Fantus.[4] To 10 drops of urine in a test tube add 1 drop of a 1 to 5% potassium chromate solution. The fluid will assume a distinctly yellow color. With the same dropper, or one of the same caliber, add drop by drop a 2.9% silver nitrate solution until a permanent and distinct color change to red-brown occurs, resulting from the formation of silver chromate. The number of drops required to produce the change of color expresses in grams per liter the chloride content of urine.

Administration of Parenteral Fluids. As patients with obstruction at the pylorus require fluid therapy in the correction of fluid and electrolyte balance, the method of administration is important. Haden empha-

* Awarded the William E. Lower Fellowship Thesis Prize for 1945.

sized the fact that in the absence of renal or cardiac failure the simplest measure of the completeness of therapy is the amount of sodium chloride being excreted by the kidneys. Surprisingly large amounts of sodium chloride are usually necessary, as much as 1 gm. per kilo of body weight, or 70 gm. for an average man of 154 pounds. If given in the form of physiologic sodium chloride solution (0.85%), about 80 liters would be required, which obviously would overtax the cardiovascular system. Therefore, 500 cc. of 3% sodium chloride solution is given intravenously at the rate of 40 to 60 drops a minute once or twice daily at the start of treatment. After the first 24 hours its administration is guided by urinary chloride determinations.

Haden[6] described the usual course. The urinary excretion of chlorides changes little for a few days, and the blood chloride level, if not low at the beginning, remains much the same. The chloride is evidently being absorbed by the tissues, and when the need of the tissues is satisfied, often a large amount (5 gm. or more) is excreted. This is the proper time for operation from the standpoint of body chemistry. After operation the secretion of chlorides again decreases but not to such a low level as was present on admission. When the reaction to the operation has ceased, usually a large amount of chloride is again excreted. This is similar to the increased excretion after the crisis in lobar pneumonia. Chloride retention by the tissues may be a protective mechanism, since patients following such a course have fewer toxic symptoms than when the supply of chlorides is inadequate. The aim is to keep the urinary chloride excretion above 5 gm. in a 24-hour period.

Since additional fluid and food are usually required by these individuals, one or two additional intravenous injections of 1000 cc. of 5% glucose in 1% sodium chloride solution may be given daily by the slow drip method at the start of treatment. If severe dehydration is present, 1800 cc. of 3% glucose in 1% sodium chloride is given subcutaneously daily until the fluid and mineral salt balance is reëstablished.

Analysis of Clinical Data. In this series of 50 cases (Tables 1, 2) of duodenal ulcer complicated by gastric retention at the time of the initial examination, 41 patients were men and 9 women. The ages ranged from 20 to 81 years. Operations were performed on 30 patients. Eight patients had partial obstruction for less than 1 year, and the remaining 42 complained of intermittent attacks of at least partial obstruction from 2 to 35 years. Gastric retention disappeared under medical management in all except 3 patients in whom pyloric obstruction was not relieved. Operation was considered advisable because of the previous history of pyloric obstruction or the presence of a persisting narrow duodenal channel as shown by progress roentgen examinations. Five patients had gastric resection and 25 gastroenterostomy. The remaining 20 patients received only medical management, which was directed towards correcting dehydration, restoring chemical balance, and relieving the obstruction. Gastric aspiration and lavage was carried out nightly until the obstruction was relieved or operation was performed.

At the beginning of treatment plasma chloride determinations were made on 48 patients. In 27 the initial plasma chloride values were above 520 mg. per 100 ml., in 13 the range was from 510 to 520 mg., and in only 8 were the values less than 510 mg. of 34 patients having CO_2 combining power determinations, in 13 the values showed alkalosis, the highest being 86.2. In 7 the values showed an acidosis, the lowest being 17.6. Blood urea determinations were done on 46 patients. In 29 the values showed a high blood urea, the highest being 201 mg. per 100 ml. Plasma protein studies done in a few cases were found to be within normal limits.

Initially all the patients had low urinary chloride values. The 24-hour urinary output was carefully measured, and only 8 patients excreted more than 1500 cc.

Roentgen examination showed that

TABLE 1.—ANALYSIS OF 30 PATIENTS HAVING PYLORIC OBSTRUCTION TREATED BY SURGERY

Case	History	Age	Sex	Duration of symptom	Duration of last attack	No. of previous attacks	Plasma chlorides	Blood urea	CO_2	Initial urinary chlorides, gm.	24 hr. urine, cc.	Roentgen rays, % retention/hr.	Total and fraction plasma proteins		No. of days medical treatment	Gastric aspirations	Total NaCl given, gm.	Final 24 hr. urinary chlorides, gm.	Final urinary output, cc.	Final plasma chlorides	Final blood urea	Final CO_2	Final blood proteins		Final Roentgen rays, % retention/hr.	Period of medical treatment	Surgical intervention
1	364,215	58	M	6 yrs.	2–3 wks.	Several	511	72	86.2	0.48	600	100/4	3.5/0.5	2.9	9	8	275	12.4	2500	544	33	65.3	7.0/3.8	3.2	None/4½	11 days	G.E.*
2	337,605	52	M	1 yr.	1 mo.	1–2	528	42	53.8	2.5	670	50/4½	...		5	5	110	16.6	1760	561	33	62.0	6.2/4.3	1.9	None/4	16 days	G.E.
3	386,932	50	M	5 mos?	2 wks.	Several	495	48	63.3	2.9	750	70/4½	...		6	5	150	10.5	2500	594	36	51.9	6.1/3.8	2.3	None/4½	10 days	G.E.
4	334,112	37	M	1 yr.	20 days	2	423	54	76.7	0.25	830	100/4	...		6	4	165	36.0	3560	..	27	57.6	7.8/5.6	2.1	None/3	Well for 3 yrs.	G.E.
5	344,266	50	M	10 yrs	7 days	Several	528	57	59 5	0.9	675	100/4½	...		5	4	100	9.3	1580	577	48	56.7	...		In 6 days none/4½	Well for 2 yrs.	G.E.
6	354,619	32	M	5 yrs.	1 mo.	Several	528	201	86.2	2.5	700	95/4	6.9/4.7	2.2	4	3	145	11.0	1460	..	33	60.5	8.7/6.5	2.2	In 5 days none/4½	10 days	G.E.
7	364,216	58	M	18 yrs.	10 days	Several	511	72	67.2	0.48	600	100/4	...		10	9	245	5.0	1750	544	51	65.3	...		In 10 days none/4½	11 days	G.E.
8	341,287	70	M	30 yrs.	1 yr.	Several	528	48	50.0	2.7	1000	60/4	...		5	3	80	6.9	1355	..	36	..	7.4/5.9	1.5	In 6 days none/4½	10 days	G.E.
9	343,165	42	F	8 yrs.	4 wks.	Several	544	45	52.8	1.9	890	80/4½	...		7	4	120	13.0	2080	528	30	59.0	...		In 6 days none/4½	10 days	G.E.
10	371,296	40	M	17 yrs.	6 mos.	1–2	495	45	17.6	0.9	1100	80/4½	...		5	4	125	4.2	715	544	..	49.0	...		...	10 days	G.E.
11	337,117	42	M	2 yrs.	2–4 mos.	Several	511	57	..	1.7	650	60/4	...		5	5	120	13.2	2060	577	27	..	...		In 5 days none/4	8 days	G.E.
12	336,213	76	M	15 yrs.	1 yr.	Periodic ev. 2 wks.	462	111	..	0.18	260	85/5	...		5	4	140	14.6	2400	528	51	..	...		In 2 mos. none/5	Well for 4 yrs.	G.E.
13	386,294	38	M	1 yr.	Few wks.	2	561	42	59.5	0.40	510	95/4½	...		6	5	150	19.2	1940	..	..	..	...		In 1 mo. none/3½	40 days	G.E.
14	353,128	69	M	5 yrs.	2 mos.	4–6 wks.	511	60	..	0.80	500	100/4	...		5	4	150	18.2	2500	..	..	..	...		In 6 days none/4	10 days	G.E.
15	341,188	34	M	10 yrs.	2 wks.	2	512	50	38.2	2.4	660	50/4½	...		6	3	150	5.7	570	..	57	...	...		In 10 days none/4½	5 mos.	G.R.†
16	366,599	29	M	3 yrs.	4–5 wks.	1	544	36	..	0.5	500	50/4½	...		5	2	150	7.9	850	..	..	..	...		...	6 days	G.E.
17	346,665	50	M	1 yr.	2 mos.	1	528	..	..	1.5	380	80/5	...		4	3	95	16.5	2300	..	..	..	...		In 6 days none/3½	8 days	G.E.
18	360,795	55	M	5 yrs.	4 days	4–5	511	42	..	0.35	350	50/4½	...		6	5	175	14.2	2875	511	33	..	...		In 50 days none/4	4 mos.	G.E.
19	374,059	54	M	7 yrs.	7 days	6	495	72	53.8	1.1	450	100/4	...		6	5	150	13.9	2385	..	45	..	...		...	7 days	G.E.
20	341,188	42	M	18 yrs.	1 wk.	Several	511	..	..	1.4	710	90/4	...		4	4	152	8.4	2080	..	..	..	...		...	9 days	G.R.
21	388,581	52	M	25 yrs.	5 days	Several	..	30	..	0.9	640	80/4½	4.5		4	2	60	7.8	650	..	..	..	4.7/3.0	1.7	...	19 days	G.R.
22	375,528	59	M	3 yrs.	Few wks.	Several	..	42	..	1.3	3850	90/4	...		6	5	251	15.2	1525	..	..	..	...		In 7 days 35/4	14 days	G.E.
23	391,998	64	M	15 yrs.	2 mos.	1	561	57	69.1	1.2	1275	100/4	...		7	7	175	4.4	1350	561	30	51.9	5.7		None/4	30 days	G.E.
24	392,058	45	M	8 yrs.	8 days	Several	544	39	53.8	0.3	900	100/4	...		4	4	125	11.6	2100	571	35	51.8	...		In 10 days 30/4	..	G.R.
25	308,267	65	F	3 yrs.	2 wks.	2	561	27	53.8	0.8	400	95/24	...		9	8	280	10.9	2100	..	..	..	...		...	14 days	G.E.
26	310.027	36	F	2 yrs.	3 wks.	2	478	60	..	0.15	370	90/4½	...		7	7	125	13.9	1580	..	..	..	...		...	8 days	G.E.
27	320,803	48	M	20 yrs.	1 yr.	3	528	45	62.5	1.5	450	90/4½	...		4	4	160	5.6	800	528	30	62.6	...		...	6 days	G.E.
28	330,128	58	M	4 mos.	2 wks.	1	561	51	48.1	1.4	900	65/4½	...		4	4	80	11.3	1170	511	54	59.6	...		...	5 days	G.E.
29	331,815	50	M	16 yrs.	2 mos.	Several	561	42	47.1	0.2	800	80/4½	...		4	4	60	7.5	800	..	..	..	6 8/4.8	2.0	None/4½	20 days	G.R.
30	318,738	57	M	12 yrs.	1 wk.	Several	495	51	65.3	1.25	625	60/4½	...		4	4	60	6.8	2400	526	42	52.6	...		...	5 days	G.E.

* G.E. = Gastroenterostomy. † G.R. = Gastric resection.

TABLE 2.—ANALYSIS OF 20 PATIENTS HAVING PYLORIC OBSTRUCTION TREATED BY MEDICAL MANAGEMENT

Case	History	Age	Sex	Duration of symptoms	Duration of last attack	No. of previous attacks	Plasma chlorides	Blood urea	CO_2	Initial urinary chlorides, gm.	24 hr. urine, cc.	Roentgen rays, % retention/hr.	Total and fraction plasma proteins	No. of days medical treatment	Gastric aspirations	Total NaCl given, gm.	Final 24 hr. urinary chlorides, gm.	Final urinary output, cc.	Final plasma chlorides	Final blood urea	Final CO_2	Final blood protein	Final Roentgen rays, % retention/hr.	Last note
31	374,112	64	F	7 yrs.	2 wks.	Several	528	105	38.5	0.9	605	65/3	6.3/4.1 2.2	4	3	70	13.7	3000	511	30	58.5	6.3/3.7 2.6	In 24 days none/4½	1942
32	357,191	81	M	35 yrs.	8 days	Several	528	69	35.7	1.18	1980	65/4½	...	3	3	85	10.9	2210	..	54	..	...	In 13 days none/4½	1941
33	308,100	52	M	30 yrs.	14 days	2	528	54	..	0.7	1400	100/4½	...	7	6	120	9.4	4000	541	30	..	...	In 7 days none/4½	1943
34	414,321	58	M	3 yrs.	2 wks.	Several	412	108	71.0	0.2	700	100/4½	...	8	7	200	18.0	4000	561	30	57.6	...	In 1 mo. none/4½	1944
35	339,715	54	M	5 yrs.	2 mos.	1	526	52	52.6	0.18	600	30/4½	...	4	2	60	16.8	2600	511	30	..	...	In 11 days none/4½	1940
36	350,163	49	M	2 yrs.	2 wks.	1	511	60	..	1.10	400	75/4½	...	7	4	150	9.1	1800	528	24	..	...	In 11 days none/4½	1941
37	350,508	54	F	15 mos.	2 wks.	1	511	60	42.2	0.4	310	70/4½	...	4	4	100	17.6	2770	561	39	50.0	...	In 10 days none/4½	1941
38	389,742	50	M	7 yrs.	4 mos.	1	545	33	60.5	0.7	800	100/4½	...	4	3	75	6.7	2000	528	30	52.5	...	In 10 days none/4½	1943
39	415,420	52	M	35 yrs.	2 wks.	Several	511	30	..	0.7	1400	100/5	...	5	5	125	9.4	4000	544	33	..	6.5	In 6 days none/3	1944
40	336,954	34	F	1 yr.	7 days	1	511	24	66.2	1.5	1500	60/4½	...	7	6	150	11.0	2200	540	28	59.2	...	In 9 days none/4½	1940
41	339,562	20	F	1 yr.	Mos.?	1	561	..	..	0.57	2370	60/4½	...	6	2	150	6.4	2100	528	..	..	...	In 14 days none/3	1940
42	339,557	68	M	3 yrs.	1 mo.	1	511	48	..	0.6	740	80/5	...	6	3	130	10.3	1300	..	..	..	...	In 15 days none/4	1940
43	300,478	36	M	7 yrs.	1 yr.	Several	544	39	44.3	0.7	2840	30/5	...	7	4	175	12.4	1480	544	30	56.7	...	10/3	1940
44	407,795	60	M	1 yr.	4 days	1	500	39	52.2	2.4	2000	35/24	...	9	9	245	9.8	2600	..	36	48.1	...	1/6	1944
45	314,304	63	F	10 yrs.	3 mos.	Several	594	60	50.1	0.53	400	25/4½	...	5	5	125	10.5	1825	..	..	..	...	Nonh/4½	1942
46	341,188	39	M	3 yrs.	2 wks.	1	561	..	..	0.93	1340	80/5	...	6	2	120	5.7	570	..	..	..	...	In 8 days none/4½	1944
47	110,952	64	M	10 yrs.	1 mo.	Several	544	27	57.0	2.0	1000	100/4	...	5	5	140	8.8	2950	511	..	..	...	None/6	1944
48	286,178	71	M	8 yrs.	4 days	2	561	45	69.1	0.29	200	90/6	...	8	8	226	9.2	2000	528	30	52.8	...	None/3½	1944
49	165,115	48	F	1 yr.	2 wks.	1	528	27	61.4	0.82	800	100/6	...	5	6	65	7.6	2600	577	27	45.3	...	None/7	1944
50	395,985	35	M	3 yrs.	7 days	1	528	24	61.4	0.8	600	60/24	...	5	4	75	8.2	2200	514	24	52.4	...	None/3½	1943

* G.E. = Gastroenterostomy. † G.R. = Gastric resection.

after 4½ hours 48 patients had more than 50% retention, and 2 had 25 to 50% retention.

Medical management varied somewhat for each patient. Some did not seem to be particularly dehydrated, but urinary chloride values were extremely low as compared with accepted normal values. These patients were given 15 to 35 gm. of sodium chloride parenterally daily, 500 cc. of 3% saline intravenously in the morning, and 1000 cc. of 5% glucose in 1% saline in the afternoon by slow drip method. This was done to restore the chloride balance as rapidly as possible without overburdening the circulatory system. Patients in whom dehydration was as important as salt depletion were given 1800 cc. of 3% glucose in 1% saline subcutaneously and 1000 to 2000 cc. 5% glucose in 1% saline intravenously daily.

The daily urinary excretion value was used as an index of treatment in restoring the chloride balance. The excretion level was always low at first, and subnormal levels persisted during the first few days of treatment. Then suddenly *regardless of the plasma chloride levels*, normal or high, chlorides were excreted in the urine. This seemed to indicate that chloride balance had been restored and that *the tissues had adequate chlorides.*

Normal chloride balance was restored in 3 to 9 days, the average being 5.

Initially all of the patients had low *urinary* chloride values. Forty patients had a plasma chloride value of 510 mg. per 100 ml. or higher. These patients required approximately the same amount of sodium chloride to bring the urinary chloride excretion values to normal as did 8 patients whose plasma chlorides were definitely lower. The important factor is that patients who received an average of 120 gm. of sodium chloride for approximately 5 days excreted during this period an average of about 20 gm. in the urine and another 20 gm. in the gastric secretion. This left a net total of about 80 gm. of retained sodium chloride; this could be considered the amount necessary to restore chloride balance.

Obviously, if plasma chloride values had been used as an index of treatment, *only 8 patients in this group would have received an adequate amount of sodium chloride.* Consequently, the 40 patients with plasma chloride values of 510 mg. per 100 ml. or higher would probably not have received any sodium chloride.

After treatment 10 patients excreted less than 1500 cc. of urine daily. This is explained on the basis of normal kidney function and high concentrated urine. With a small amount of fluid the kidney, because of its concentration power, excreted more salt in the urine.

All plasma chloride values were normal after the treatment. Both the alteration in total non-protein nitrogen content of the blood and the disturbance of the acid-base balance at the beginning of treatment returned to normal after the chloride balance had been restored.

Roentgen examination showed that in 36 patients the obstruction was completely relieved. Four had minimum retention, and 10 did not have further roentgen examination because operation was performed immediately after restoring chemical balance. There was no gastric retention 2 days before operation in 7 of these 10 patients. In the remaining 3 patients the pyloric obstruction was not relieved by medical management.

From a review of the 50 cases it is obvious that regardless of the age of the patient or the history of previous pyloric episodes, *a 5-day trial of adequate medical management is required in order to know the degree of cicatricial stenosis of the pylorus.* In 20 patients in whom pyloric obstruction was caused by spasm or inflammatory edema, medical management proved satisfactory.

Discussion. 1. *Hypochloremia.* There are several approaches to the problem of salt replacement in patients with high intestinal obstruction. In the past the method of trial and error was used by the clinician, who, after determining the

plasma chloride concentration, gave the amount of salt he supposed the patient needed. To see how accurately he had estimated the patient's requirements, he again determined the plasma chloride level.

This method has several faults: (1) If the plasma chloride concentration is determined too soon after saline administration, misleading values will be obtained. (2) If the salt need of the patient is underestimated, valuable time will be lost. (3) Excessive salt administration will not be shown by an abnormally high plasma chloride level, because the excess is excreted in the urine. Often in sick patients, as shown in several of the patients presented, the level cannot be raised to the lower limits of normal. In these, if the clinician uses only the plasma chloride level as an index of overdosage of salt, he is likely to be misled into forcing salt upon patients unable to attain a normal plasma chloride level at the time.

Bartlett, Bingham, and Peterson[1] showed that hypochloremia could be prevented by replacing abnormal fluid losses with equal volumes of physiologic saline solution, the amount of which was determined by means of a formula, which will be explained later. When losses were replaced with an equal volume of Ringer's solution, a fairly satisfactory plasma chloride level was obtained. However, the daily urinary excretion of salt fell below normal, indicating that an insufficient amount of salt had been administered.

The use of the volume for volume rule makes it necessary that the patient be under the physician's care when loss of body salt is initiated. Many times the patient loses an unknown amount of salt-containing fluid before consulting a physician, and therefore the volume for volume rule cannot be applied.

Based on the assumption that the plasma chloride level is a satisfactory index of chloride concentration in the body, Bartlett, Bingham, and Peterson[1] developed a formula referred to previously for calculating the salt requirement of patients with hypochloremia. According to their formula it may be assumed that approximately 20% of body chloride has been lost when the plasma chloride level is 20% below normal. When the normal salt content of the body (0.248% of body weight) and the lost portion of salt, as indicated by the plasma chloride level, are known, the number of grams of salt needed to restore chlorides to normal is calculated as follows:

$$\text{Normal} = \frac{\text{Normal plasma chloride} - \text{actual plasma chloride}}{\text{Normal plasma chloride}} = 0.0248 \times \text{body weight (gm.)}$$

For clinical purposes this formula was somewhat cumbersome, and a simpler rule was made. The patient will receive 0.5 gm. of salt per kg. of body weight for each 100 mg. required to raise the plasma chloride level to normal.

However, in using this clinical rule certain complicating factors must be considered: (1) The plasma chloride content is preserved at the expense of the tissue chloride, so that the amount of chloride in the blood may be normal, while the tissue chlorides are depleted. In such cases chloride deficiency is not indicated by plasma chloride values alone. (2) If a patient's dehydrated weight is used in calculating his salt requirements, less salt will be given than if his hydrated weight is used. (3) Dehydration tends to concentrate the blood, which in turn raises the plasma chloride level. If the salt needs are calculated on the basis of this plasma chloride level, the amount of salt given will be less than if the levels are calculated when the blood is not concentrated. (4) If sodium and chloride ions are lost in equal proportions, or if sodium ions are lost in excess of chloride ions, a certain amount of water is also eliminated in the effort to keep the sodium concentration and the osmotic pressure of the body fluids constant. Under these circumstances the plasma chloride concentration may be normal, although loss of sodium and chloride is significant. Thus the plasma chloride level does not accurately indicate the salt needs of the body.

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In attempting to calculate the need for chlorides by plasma chloride determinations the following difficulties and inaccuracies are apparent: (1) Salt loss cannot be replaced by the volume for volume rule because it cannot be accurately measured. (2) The formula and clinical rule depend upon factors which are quite variable. (3) Although the plasma chloride level can be determined at frequent intervals and salt given as indicated, this method does not invariably insure the maintenance of an adequate salt balance because plasma chloride values are not always a true indication of the salt requirements.

On the other hand, *urinary chloride determinations are simple and give the most accurate indication of chloride needs.* As long as the patient excretes from 5 to 10 gm. of salt a day in the urine, there is no danger of tissue salt depletion. It is well known that after a few days of deficient salt intake, the kidneys show a remarkable ability to conserve the salt remaining in the body, and the urinary salt excretion drops to less than 0.5 gm. a day. Throughout this period there may be no significant alteration in plasma chloride concentration. Sometimes the body loses salt by an abnormal route, the plasma chlorides drop below normal, and the salt content of the urine generally becomes less than 1 gm. per day. When salt is given in excess of tissue needs, large amounts of salt are excreted in the urine. Gamble[5] pointed out that if water and sodium chloride are abundantly supplied, normal kidneys will correct the acid-base balance of the plasma by excreting the ion not needed by the body. As shown by Haden and Orr,[9] chlorides other than sodium chloride are unsatisfactory for correction of hypochloremia. Therefore, urinary chloride determination is more practical for ascertaining the correct salt balance of the body.

2. *Disturbance of the Acid-base Balance.* Diminution in plasma chloride concentration with its attendant alteration of electrolyte distribution and acid-base balance is one of the most significant metabolic features of pyloric obstruction.

Loss of excessive quantities of water from the body is associated with the consequent loss of proportional amounts of electrolytes, because the body fluid concentration must be maintained within narrow limits. In dehydration due to excessive vomiting large quantities of hydrochloric acid are lost from the stomach. As a result of the loss of Cl ions from the blood, an excess of base, chiefly sodium, is retained in the form of bicarbonate. In this way neutral salt (NaCl) is replaced by an alkaline salt ($NaHCO_3$), which results in alkalosis. *Thirteen cases in this series corroborate this statement.*

The inanition and carbohydrate deficiency which accompany continued vomiting may contribute to the production of alkali deficit because of associated starvation ketosis. The liver preferentially burns carbohydrate, but in its absence fat and protein are oxidized at excessive rates. When this occurs, ketone bodies and glucose as end products of fatty and amino acid oxidation in the liver are liberated into the blood stream and utilized by extrahepatic tissues. However, the rate of production may exceed that of utilization, and an accumulation occur in the blood and give rise to ketosis.

In 7 of our cases there was little hydrochloric acid in the gastric juice. Continuous vomiting produced dehydration, which resulted in acidosis demonstrated by a fall in the CO_2 combining power. Maybe the ketone acids resulting from starvation in the pyloric obstruction partly offset the bicarbonate increase produced by loss of chloride.

3. *Increase in Non-protein Nitrogen Constituents or urea of the whole blood.* Alteration in the blood urea content of the blood in 29 cases of pyloric obstruction was due to two factors: (1) Excessive vomiting and consequent dehydration make a minimum amount of body fluid available for renal excretion. Since a certain dilution is necessary for their elimination, nitrogenous substances of the blood

are retained in proportion to the degree of oliguria, which sometimes is extreme. (2) Dehydration due to water privation (vomiting and gastric lavage) after 42 hours and starvation alter and increase the rate of protein metabolism, which results in catabolism. This is commonly regarded as toxic destruction of protein. The increase in the level of blood urea, which occurs under such circumstances, is due to the *combined effects of catabolism and dehydration.*

Safety Factors. Cutting, Lands, and Larson[3] concluded that cats could tolerate the rapid intravenous administration of large amounts of sodium chloride solution if the solution was not more concentrated than 2%. The lethal amount is approximately 500 cc. of 1% solution per kg. of body weight when the injection is made at approximately 5 cc. per kg. of body weight a minute. Translated into terms of a human being weighing 70 kg., or 154 pounds, this amounts to a total of 35 liters of 1% solution given at the rate of 350 cc. a minute. The quantity of fluid and speed of injection is greater than that used in clinical practice. Within 24 hours of administration of this large infusion of 1% sodium chloride, about 80% of the water and almost all the salt were eliminated by the kidneys. Indeed in almost half of the animals more sodium chloride than was injected was excreted.

In a series of patients Milbert[11] used hypertonic solutions (5% sodium chloride, 10% glucose, and so forth) at the rate from 57 to 106 cc. a minute, which exceeded the accepted limits of safety.

Hypertonic saline solution (3% sodium chloride) was used routinely in our cases. The slow drip method was used, 40 to 60 drops per minute. Urinary chloride excretion and output of urine were checked daily. The urinary chloride values were less than 5 gm. daily at the start of treatment, regardless of administration of 15 to 35 gm. of salt. The quantity of urine excreted was less than 1500 cc. in 45 cases. Both output of urine and urinary chloride values were increased gradually until normal values were acquired at the end of the treatment (average 5 days).

Therefore, 3% sodium chloride is not contraindicated because of its hypertonicity. The results obtained in these cases show that an adequate salt balance can be obtained in an average of 5 days, when urinary chloride excretion value is used as an index of treatment.

Summary and Conclusions. 1. For the accurate appraisal of chloride balance in 50 cases of duodenal ulcer with obstruction, the plasma chloride determinations were found to be less reliable than the more simply performed urinary chloride determinations.

2. In 80% of the cases there was marked diminution in urinary chlorides, although plasma chlorides were normal at the time of the initial examinations. This resulted from depletion of tissue chlorides, which maintained a normal level in the blood.

3. In 60% of the cases there was severe alteration in the acid-base balance of the blood. Forty per cent had alkalosis and 20% acidosis.

4. Azotemia was present in more than 60% of the cases.

5. Hypochloruria together with nitrogen retention and disturbances in the acid-base balance constitutes the outstanding biochemical feature in patients having pyloric obstruction.

6. In patients with pyloric obstruction the necessity for supplying sodium chloride and water is well established.

7. In administering large amounts of salt 3% saline solution is preferred. The quantities of salt needed are indicated by urinary chloride determination.

8. Acid-base balance and chloride balance with normal values of blood urea were obtained after a period of approximately 5 days. During this period adequate amounts of water and sodium chloride were administered.

9. Twenty patients were relieved of pyloric obstruction by medical treatment alone. Thirty patients were treated surgically after the acid-base balance was restored by medical treatment. The proper

time for surgical intervention from the chemical standpoint was determined by a normal urinary chloride excretion (more than 5 gm. in 24 hours).

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ROENTGEN STUDIES OF THE SPLEEN

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These studies were carried out in an effort to arrive at an objective and more accurate method for determining the size of the spleen. Clinicians have long realized the limitations of physical examination in evaluating the size of this organ. Although it has long been a common practice to attempt to visualize the spleen by roentgen ray, no definite criteria have been established for interpreting the roentgen shadow.

It is realized by all physicians that some enlarged spleens are not palpable. This may be due to obesity, tense or well developed abdominal muscles, a narrow costal angle, or most often, a high diaphragm. On the other hand, it is not realized by many physicians that some palpable spleens are not enlarged. These spleens are often palpable only because of a lax abdominal wall, wide costal angle, malnutrition, or most frequently, a low diaphragm. Satisfactory roentgen criteria for spleen size will obviate many unnecessary and time-consuming diagnostic procedures in such instances.

Case Material. During the last 18 months, over 300 patients in an Army General Hospital have had roentgenograms made of their spleens. Most of the subjects were young men; 50% had palpable spleens or diseases which might cause splenic enlargement. The majority of this group had, or had had malaria. A moderate number of cases of cirrhosis of the liver, hepatitis, and infectious mononucleosis, and isolated cases of thrombocytopenic purpura, congenital hemolytic jaundice, leishmaniasis, sarcoidosis, Hodgkin's disease, leukemia, and so forth were studied. The remaining 50%, the control group, consisted of neuropsychiatric, general medical and surgical patients, with no indication of any disease which might cause splenic enlargement.

Technique. Postero-anterior films are taken before meals since a full stomach may interfere with visualization of the organ; no other preparation is employed. The plates are made in the PA projection, using the Potter-Bucky diaphragm, 100 milliamperes, with a time exposure of 0.5 second, at a target film distance of 36 inches. The kilovoltage varies with the thickness of the patient and averages 6 to 8 kv. less than the usual stomach technique. The central ray is directed through a point halfway between the midline and the left lateral chest wall, three finger breadths below the ensiform cartilage.

Interpretation. During this study, it became obvious that there was considerable variation in the size of normal spleens in different individuals, although the spleen size remains constant in a given individual. It appears, in general, that the size of the spleen varies with the size of the individual, although no definite relationship has been established. According to Gray's Textbook of Anatomy, the normal spleen in an adult is about 12 cm. in length, 7 cm. in breadth, and 3 to 4 cm. in thickness. Due to the oblique position of the spleen, the width of the roentgen shadow is a combination of the anatomical breadth and thickness. A spleen that is visible in both its length and width presents no problem in menstruation. It is rarely found, however, that the spleen is visible in its entire length, whereas it is always possible to determine its width. The width is measured at the broadest visible point of the shadow, which is usually just below the hilus. It is measured to the outer border of the spleen, when this is visible, or the internal surface of the ribs, when this border is not visible.

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The length of the spleen can be determined in only a small proportion of patients, due to inability to make the upper portion of the organ visible. It was found in those cases where the upper pole can be visualized, that there is no constant relationship of the position of the spleen to the diaphragm. Thus the diaphragm cannot be used as a point from which to measure length.

Any rotation of the spleen on its long axis will alter its width, whereas rotation on its horizontal axis will alter its length. In doubtful cases, films taken in the A.P. left oblique may be of value. When rotation decreases either of these diameters, there must be a corresponding increase in density. Density, therefore, must be taken into consideration in determining spleen size, and is measured by comparing the spleen with the lower half of the left kidney. The density is considered increased if greater than that of the normal kidney. There was no evidence of renal disease in any patient in this series.

Using this technique, the lower pole of the left kidney is nearly always visible, and often its entire contour can be seen. The measurements of the kidney, as given in the standard text mentioned above, are $11\frac{1}{4}$ cm. in length, 5 to $7\frac{1}{2}$ cm. in breadth and $2\frac{1}{2}$ to 3 cm. in thickness. The spleen and kidney, therefore, are of comparable size and the relationship of the size of the kidney to that of the spleen is the ideal method for determining splenic enlargement. In the majority of films, however, this criterion cannot be used because the complete contour of both organs cannot be seen. When the complete contours can be seen, any spleen which is more than 85% the size of the kidney is regarded as enlarged. (The reason for arbitrarily using 85% in this comparison is that the magnification of the kidney is greater than that of the spleen in this projection.)

Thus the factors of width, density, and comparison with kidney size are used to determine the size of the spleen. The length of the spleen is infrequently found to be of value because of inability to visualize the upper pole. In obscure cases, artificial pneumoperitoneum might be used to more clearly outline the spleen, particularly the upper pole; the authors have had no experience with this method.

Criteria. Only the factors of width, density, and comparison with kidney were used to establish these criteria. The size of the normal spleen was determined through study of the large series of controls. Normal spleen roentgenograms are shown in Figure 1. All patients were carefully followed clinically and much time and effort were expended in studying the spleen shadows. The following criteria were established:

1. The spleen is not enlarged if it is: (*a*) not visualized; (*b*) less than 5 cm. in width; (*c*) less than 85% the size of the kidney.

2. The spleen is enlarged if it is: (*a*) more than 6 cm. in width; (*b*) more than 85% the size of the kidney.

It is at once apparent that spleens from 5 to 6 cm. in width are not included in these criteria. In such instances, density is the deciding factor. Spleens from 5 to 5.5 cm. in width are not enlarged if their density is normal, but are questionably enlarged if their density is increased. Spleens from 5.5 to 6 cm. in width are only questionably enlarged if their density is normal, but are definitely enlarged if their density is increased (Table 1).

Results. There were relatively few splenic shadows which fell into the questionable group. In the vast majority of cases, the size of the spleen could be definitely and readily determined from the roentgenogram.

In the majority of cases where the spleen was palpable, roentgen examinations showed splenic enlargement, using the above criteria. These included patients with malaria, infectious mononucleosis, cirrhosis of the liver, leishmaniasis, and congenital hemolytic icterus (Fig. 2).

In 17 instances where the spleen was palpable, roentgen examinations showed no splenic enlargement, and obviated extensive laboratory studies. These included

patients with psychiatric disorders and unexplained fever (Fig. 3). None of these patients were explored or autopsied, but the clinical course of each was compatible with the roentgen diagnosis.

culty can be surmounted only by taking films at frequent intervals. All of these men had very low diaphragms, with wide costal margins, rendering the spleen more readily palpable.

TABLE 1.—A SUMMARY OF CRITERIA USED

Interpretation	Width	Density
Normal	Less than 5 cm.	Normal or increased
	5 to 5.5 cm.	Normal
Questionably enlarged	5 to 5.5 cm.	Increased
	5.5 to 6 cm.	Normal
Enlarged	5.5 to 6 cm.	Increased
	More than 6 cm.	Normal or increased

Any spleen less than 85% the size of the kidney is not enlarged; any spleen more than 85% the size of the kidney is enlarged.

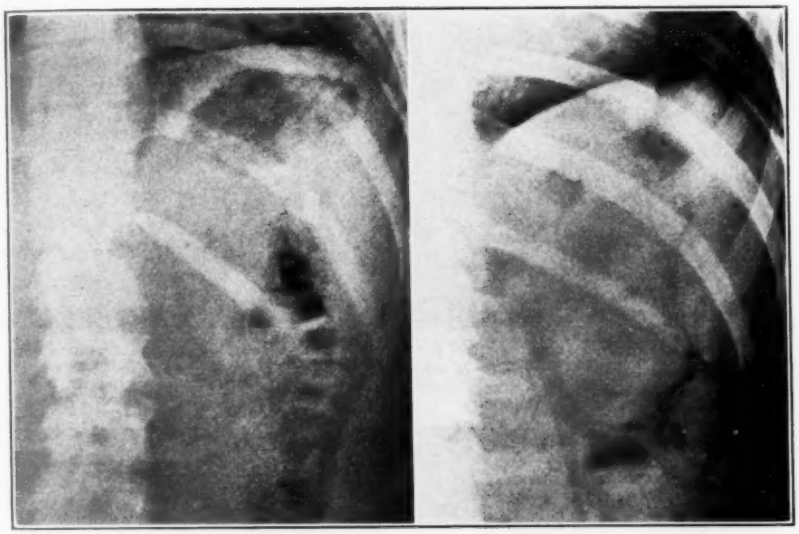

FIG. 1.—Normal splenic shadows in normal individuals. *Left*, less than 5 cm. in width. *Right*, less than 5.5 cm. in width, and not increased in density.

Five patients with a history of malaria did not have palpable spleens, and showed no enlargement of the spleen on the roentgenogram when they first came under observation. They later developed malaria, and a palpable spleen. The size of the spleen increased on the roentgenogram but was still within the normal limits established with the above criteria (Fig. 4). These patients evidently had very small normal spleens, which enlarged. It is quite possible that spleens which are not enlarged by our criteria, are indeed enlarged for that particular individual. This diffi-

Seven cases, 4 of malaria, 2 of cirrhosis of the liver, and 1 of thrombocytopenic purpura, did not have palpable spleens; but roentgen examination showed definite enlargement. The last of these underwent splenectomy, and the spleen was slightly enlarged, weighing 230 gr. after removal. It should be remembered that during delivery of the spleen at operation, a certain amount of blood may be squeezed out; so that this spleen may have weighed considerably more *in situ*. Three of the 4 patients with malaria developed palpable spleens when they developed clinical at-

tacks of malaria (Fig. 5). In the remaining 3 cases, the spleen could not be felt at any time.

Eight cases with normal sized spleens were studied to determine the effect of food, rest and moderate activity on the spleen size. Films were made shortly after arising, 1 hour after breakfast, before midday dinner, and 2 hours after dinner. The patients carried on the normal activities of ambulatory hospital patients. These patients were also studied at weekly intervals for 1 to 3 months. No change in spleen size was found.

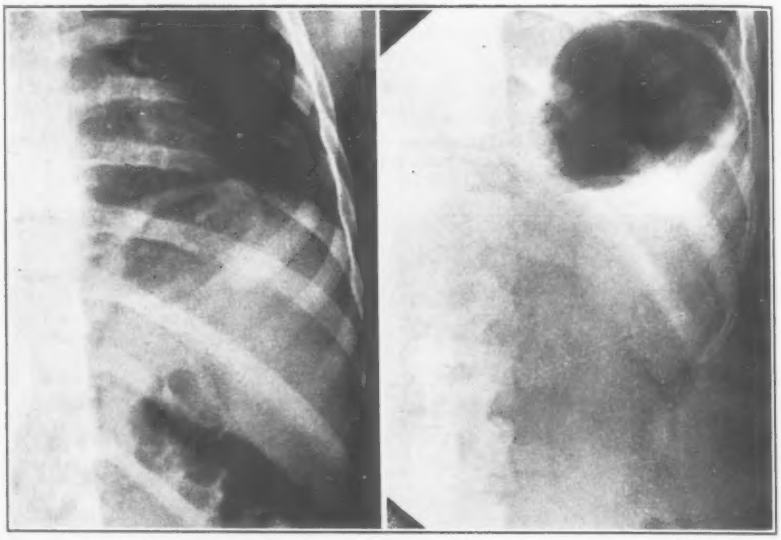

FIG. 2.—Enlarged palpable spleens. *Left*, 7.5 cm. in width (infectious mononucleosis). *Right*, 8 cm. in width (malaria).

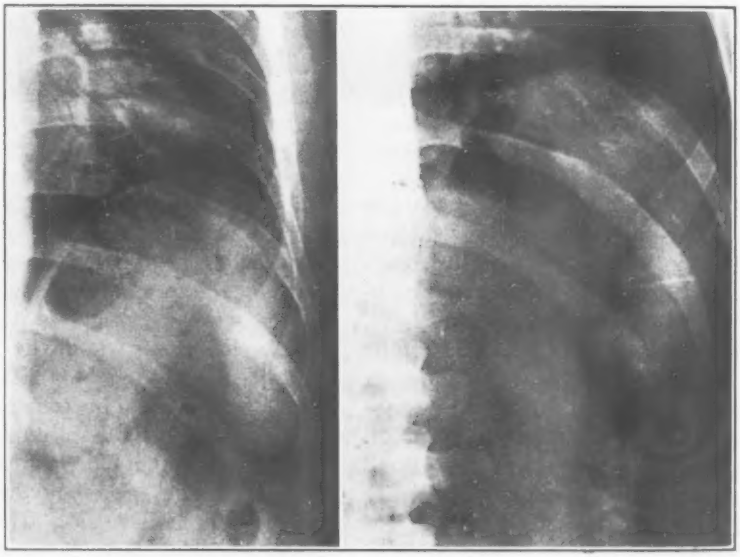

FIG. 3.—Normal patients illustrating palpable spleens which are not enlarged. Both spleens are less than 5 cm. in width.

Six cases with readily visible splenic shadows, who were recovering from recent attacks of tertian malaria, were studied before and after adrenalin. Films were made immediately before and 1, 5, and 15 minutes after the injection of 0.5 cc. of 1 to 1000 adrenalin subcutaneously. The patients remained in the same position for all 4 films, and practice gave approximately the same position of the diaphragm in expiration. Four of the patients showed a marked decrease in spleen size, as illustrated in the accompanying diagrams (Fig. 6).

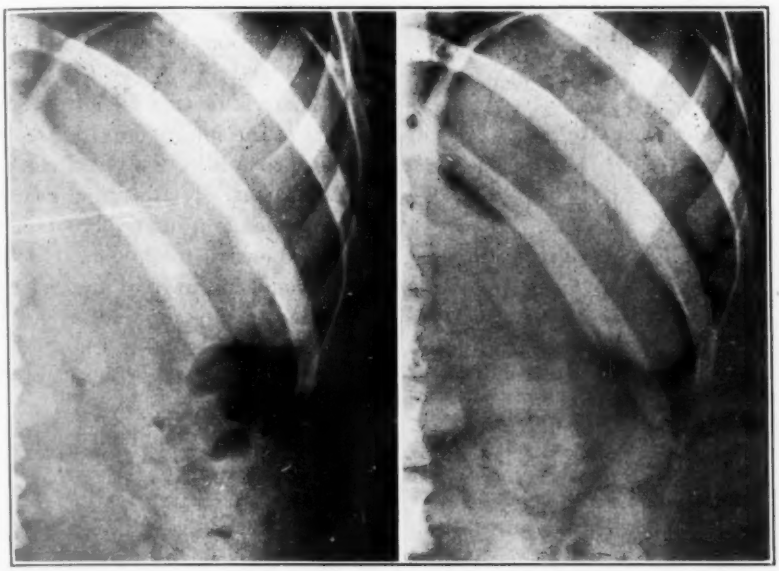

FIG. 4.—A spleen enlarged for an individual but still within normal limits by these criteria (see text). *Left*, less than 5 cm. in width. *Right*, 5 cm. in width, and of normal density.

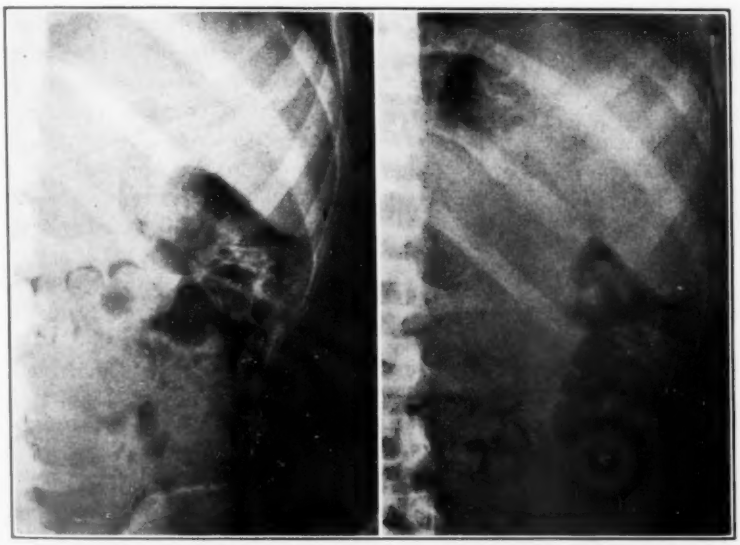

FIG. 5.—An enlarged spleen, *left*, which was not palpable. Five days later, *right*, during clinical malaria, spleen became larger and was palpable.

Summary. 1. A simple technique for roentgen examination of the spleen is described.

2. An attempt has been made to establish criteria for determining splenic enlargement.

FIG. 6.—Composite tracings of spleen shadows, showing decrease in size after injection of adrenalin. ———— before injection of adrenalin. . . . . 15 minutes after injection of adrenalin.

3. These criteria depend upon the width, density, and relation to kidney size.

4. It is highly desirable that tables be worked out for determining the size of the normal spleen in relation to body height and weight.

5. There seems to be no diurnal variation in the size of the spleen, and no variation in relation to ingestion of food or moderate activity.

6. There is often a definite decrease in the size of the spleen, 5 to 15 minutes after subcutaneous injection of adrenalin.

Conclusions. 1. Roentgen examination of the spleen is a relatively simple, rapid, and inexpensive method that determines enlargement in the great majority of cases.

2. Many palpable spleens are not enlarged.

3. Many enlarged spleens are not palpable.

EMOTIONAL FACTORS IN OBESITY

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The obese person has no desire to be told that he eats too much or that his organs are normal; instead he wishes to be told that he has a "gland trouble" and that he will have to take medicine to correct this. The physician often complies with his wishes and treats him with various substances, some harmful, while others do not harm particularly but are hardly more than placebos.

It is generally agreed that within limitations the laws of thermodynamics are applicable to the body and that obesity is due to "an over-all intake of energy which has exceeded the total dissipation of energy of the body, *i. e.*, a positive energy balance."[8] Therefore, any form of therapy must consist of either a decrease in the energy intake or increase in the energy output. With rare exceptions it is not feasible to increase the energy output of an individual to the extent that obesity may be prevented or relieved. The therapy which should prove more efficacious and which should receive the attention of the patient and physician alike is the decrease in energy intake. Marked restriction of the caloric intake will alone cause a loss of weight, and the more accepted method of restricting the caloric intake is by giving the patient a calculated diet. Such diets may vary from 500 to 1500 calories. The experience in this and other clinics has shown that the incidence of failure is quite high when diet therapy is used alone.

Many observers[1,2,5,8,10] have emphasized the fact that this desire for excessive food consumption is based on a disturbance in the psychologic make-up of an individual and that the stimulus is not derived from an abnormally functioning organ, but no reported studies can be found in which patients were treated by means of psychotherapy alone. This study was arranged to evaluate this form of therapy.

Materials. To obviate the economic and educational factors that are met with in an Out Patient Metabolism Clinic, it was decided to include in this study only the patients admitted to the Private Medical Clinic of Duke Hospital. All were under the direct supervision of the writer. The primary complaint was obesity or "nervousness" and frequently other complaints, such as hypertension, menopause, etc., were present. Complete physical examination and laboratory studies, including study of the blood and urine, basal metabolic rate, Roentgen ray of the skull, renal function, and electrocardiograms were made on the initial entrance to the hospital. Only those patients who were able to be up and attend to their duties were included in the study. All patients were 10 kg. or more over their calculated ideal body weight. Women in the menopause age were included. Patients with diseases commonly associated with obesity, such as given in Table 2, were not used in the experiment.

The weights were obtained by the same observer using the same balances for each determination, except in 6 instances when these data were supplied by the patient's home physician. On each return visit a blood pressure reading was obtained, the hemoglobin estimated, the basal metabolic rate determined and the urine examined, particularly for acid bodies.

A total of 93 patients were studied. These patients are divided into the following 4 groups:

Group 1. Thirty-eight patients were treated in the following manner: A detailed inquiry was made as to their developmental history, social and sexual adjustment, economic status, relationship to their family and friends and other factors that may have had influence on their

personality. An attempt was made at superficial psychotherapy which consisted of reassurance and interpretation. No calculated diet was given; however, an explanation of energy exchange and the caloric value of certain common foods was offered. Care was taken to explain the phenomenon of water retention in order to anticipate the periods during which no weight loss occurred. Instructions for keeping a food diary (measured) for 3 days previous to the clinic visit were given. No medication was prescribed in any instance.

Group 2. Thirty-five patients were given a calculated diet of 800 calories. An experienced dietician explained the diet to the patient and, when desired, on return visits further instructions were given by the dietitian. No medication was given and no effort at psychotherapy was attempted.

Group 3. Ten patients were given 5 mg. of amphetamine sulphate 3 times a day. No psychotherapy was attempted and no calculated diet was offered.

Group 4. Ten patients were handled as those in Group 3 except that thyroid substance was administered instead of amphetamine.

Results. In each of the 93 patients it was possible to demonstrate some emotional problem. For the most part, the type of psychoneurosis observed was varying degrees of tension state, characterized by afternoon occipital headache, vague gastro-intestinal symptoms, etc. Others had anxiety attacks, with excessive sweating, coldness of hands and feet, palpitation, etc. In some instances definite obsessive compulsive neurosis was observed. In the more severe emotional reactions the aid of a psychiatrist was obtained and in no instance was a patient with a psychosis treated. One of the most frequent precipitating factors during the past 4 years was worry over a member of the family in the armed services. No relationship was found to exist between the severity of the psychoneurosis and the weight of the patient.

An example of the less severe psychoneurosis is illustrated by the following patient:

O. M., a 28 year old white female, had maintained constant weight at 52 kg. since the age of 15 years. Her husband was inducted into the armed services and while stationed in this country there was no variation in the patient's weight. After her husband was sent on foreign service and had participated in several battles the patient developed the habit of eating between meals and at bedtime. Her weight increased 27 kg. in 8 months to 79 kg. The patient was seen in consultation at this time and an attempt was made to explain to her the reasons for her increased consumption of food. Her weight decreased 3.5 kg. in 4 weeks but did not progress beyond this level, however, until her husband was sent back to this country, she then lost weight down to 55 kg. where it has remained. Discussions were held with the patient relating to the caloric value of foods, but no calculated diet was offered.

A more severe type of reaction is illustrated in the following record:

C. K. G., a white, male merchant, aged 39 years, was admitted to Duke Hospital because of attacks of weakness that were associated with palpitation, sweating, fear of impending death and fear of crowds. He stated that he had always been highly excitable, given to worry over details which frequently resulted in marked insomnia. Three years previous to admission he was crossing the street at a crowded intersection when a car struck and seriously injured his small daughter. Immediately after this episode he experienced marked anorexia, nausea and vomiting. He refused food for 3 days, at the expiration of which time he was told that his child would recover completely. He then noticed that he would refuse to cross the street at the scene of the accident and in a short time began to dread crossing any street whether there was little or no traffic. At this time he developed anxiety attacks characterized by weakness, palpitation and sweating. These would occur immediately after crossing a street, and he found that if he ate something, usually a cold drink with crackers, he would experience immediate relief. When crossing the street, he had an impulse to throw himself in front of cars.

His total food intake increased to the point that, according to his food diary, it was estimated 3400 calories per day. In a period of 6 months his weight increased from a previously maintained level of 80 kg. to 102 kg. Upon admission to the hospital the physical examination, laboratory studies, including basal metabolic rate, Roentgen ray of the skull and chest, were normal. A psychiatric consultation was requested and psychotherapy was instituted. The patient was relieved of his attacks and the weight decreased to 85 kg. in 2 years, where it has remained. No calculated diet or medication was given.

All patients in Group 1 were followed for 1 year or more and 5 patients have been followed for 3 years. There was a total of 38 patients in this group, 28 females and 10 males. The youngest patient was 15 years of age, the oldest 78. Ten patients were between the ages of 30 and 40 years and 12 between the ages of 40 and 50 years. A family history of obesity was present in 14 instances.

Thirty-five patients showed weight loss in 2 weeks; in 1 instance a man weighing 181 kg. lost 6 kg. in this interval. The 3 patients who failed to lose weight in the initial period deserve more comment. One was a man 69 years of age who had been existing on a daily diet of 1 quart of whiskey, "vitamin pills," and meat for many years. He showed no interest in losing weight, and 1 year later had gained from 172.7 kg. to 175 kg. The other 2 patients were over 70 years of age and decided that they did not care to reduce their weight.

The immediate weight loss is of little importance unless the weight is maintained at the lower level. Arbitrarily, therefore, it was decided that unless a patient had maintained a weight loss of 5 kg. or more for 1 year, or if any relapses occurred after a year, the experiment was a failure. Of the 35 patients who showed prompt weight loss, 9 were considered failures by these criteria; indeed, 8 actually gained weight.

Twenty-one patients in this group had an elevation of the systolic blood pressure above 160 mm. Hg. In 14 of the 21 patients the systolic pressure was lowered by 20 mm. Hg or more. The reduction of the blood pressure accompanied the initial weight loss during the first 6 months of the experiment. After this period there was a gradual rise of blood pressure in 12 of 14 patients, so that at the end of 18 months it had risen to the level observed initially. The diastolic pressure followed the same trend as did the systolic, but not to the same degree. In 2 patients the fall in blood pressure remained constant for 2 years or more.

The patients in Group 2, treated by diet alone, were used as controls. A total of 35 patients were followed for a year or more, 12 males and 23 females. The age groups compare roughly with those in Group 1; 1 patient was 16 years of age, 1 was 72, 12 were in the 30 to 40 year group, and 14 were from 40 to 50 years of age. A family history of obesity was present in 11 patients. All patients in this group lost weight varying from 1 to 3 kg. within the first 2 weeks but by the end of the first year there were 26 failures and 9 who had maintained the weight loss of 5 kg. or more. At the end of 2 years, 5 had not gained weight, 3 had gained to the initial weight, and 1 patient could not be located. Five patients lost 30 kg. or more with no deleterious effect upon their sense of well being or their general health.

Of the 9 patients whose treatment had been considered successful only 2 had hypertension and no appreciable effect was noted in either of them.

The patients in Group 3, who received 5 mg. of amphetamine sulphate 3 times a day, showed weight loss for the first 4 weeks; after this interval there was a slow gain back to the initial weight. This was true although the drug was continued and in 6 patients the dosage gradually increased to 10 mg. 3 times a day.

The patients receiving thyroid substance (Group 4) showed no appreciable weight loss until dietary measures were instituted. The amount of thyroid substance admin-

istered was sufficient in each instance to produce untoward symptoms.

A comparison of the 4 groups is summarized in Table 1.

Because of the frequent association of obesity with disease of the endocrine system and because of the reported experimental work on animals in which obesity occurred after producing lesions in the hypothalamus, the records of 88 patients, with a diagnosis of some endocrine disease, encephalitis or inactivity due to chronic illness, were examined. These results are given in Table 2. The 2 patients with hyperinsulinism had a gain in weight of 17 and 24 kg. respectively. They had learned that an attack of unconsciousness could be prevented by eating food. In the other diseases listed, in most instances the onset of obesity antedated the diagnosis of the condition.

TABLE 1.—RESULTS WITH DIFFERENT TYPES OF THERAPY

	Total No. patients	Successful	Failures
Psychotherapy: No calculated diet	38	26	12
Calculated diet only	35	9	26
Amphetamine only	10	0	10
Thyroid substance only	10	0	10

TABLE 2.—RELATIONSHIP OF OBESITY TO ONSET OF VARIOUS MALADIES

	No. cases	Obesity present	Obesity antedating onset of illness
Myxedema	15	6	4
Cushing's syndrome	3	2	2
Hyperinsulinism	2	2	0
Pituitary tumors, including cysts	12	5	2
Menopause	30	20	18
Inactivity due to debilitating illness	10	6	2
Encephalitis (postinfectious)	16	4	0

Discussion. While this study was not planned with the purpose of establishing a single etiology for the increased food consumption that characterizes the obese individual, it is believed that the results presented establish the fact that emotional tension and psychoneurosis will in certain people produce obesity. In no patient observed by the writer has the etiology proved to be other than an excessive desire for food, and in some instances a well defined phagomania was present. In all but 5 or 6 of a group of 50 patients studied by Schopbach and Matthews[10] psychogenic factors bore a close relationship to the onset and development of obesity.

In experimental animals obesity has been produced by injury to the hypothalamus,[7] but there is no proof that lesions in this area will produce obesity in man. Greene[6] has analyzed a group of patients with diseases of the endocrine glands, suprasellar tumors and chronic encephalitis and has found that the incident of obesity in these conditions was little if any higher than patients with some other injury or disease that necessitated inactivity. An analysis of 88 patients in this clinic with a diagnosis of some endocrine disturbance, inactivity due to illness or encephalitis agrees with Greene's[6] report. The fact that patients with encephalitis do not develop obesity does not necessarily argue against the theory that lesions of the hypothalamus will produce obesity since the lesions of encephalitis need not involve that part of the hypothalamus that affects the appetite.

The efficacy of the treatment outlined in this report, that is psychotherapy, cannot be denied. Danowski and Winkler[4] reporting on the long term treatment of obesity by means of calculated diets only have reported that about 80% were failures. The number of failures in the control group reported here approximate those of Danowski and Winkler; however, the number of failures in the group that received psychotherapy alone were con-

siderably fewer. Gray[5] has stated, "The treatment of obesity depends more on the mind than on the body." In the light of the material presented in this study we agree with the above statement.

As to the administration of drugs, it has been our experience that the patient is inclined to rely upon the drug rather than upon himself. His attitude is that so long as he takes a pill extra food will not affect his weight. Cutting[3] has shown that amphetamine, propadrine hydrochloride and belladonna are of little aid in the control of obesity; however, he was more successful with thyroid substance than reported in this study. Pelner[9] has advocated the use of amphetamine but emphasized that establishment of proper good habits is necessary before maintenance weight loss is produced.

Summary and Conclusions. 1. The effect of psychotherapy without the use of calculated diets has been studied in 38 obese patients, and the results compared with obese patients treated by means of calculated diets, amphetamine and thyroid substance.

2. Psychotherapy resulted in a higher percentage of successful results than other methods studied.

3. All obese patients studied were found to have some type of psychoneurosis in varying degrees.

4. Psychotherapy and re-establishment of proper dietary habits is essential for permanent weight reduction.

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THE VALUE OF SPERANSKY'S METHOD OF SPINAL PUMPING IN THE TREATMENT OF RHEUMATIC FEVER AND RHEUMATOID ARTHRITIS*

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Rheumatic fever and its sequelæ constitute a serious problem, particularly in the Scandinavian countries, Great Britain and the United States. This disease attacks chiefly children and young adults, who should be important economic assets. In Sweden, where the disease is notifiable, it is apparent that every year there are from 1500 to 2000 new cases per 1,000,000 of the population, while in the United States, Cecil[4] states that 170,000 cases (more than 800 per 1,000,000) are reported annually.

The etiology of rheumatic fever is still unknown. Streptococci, septic foci, bowel intoxication, malnutrition, climatological factors and allergy, each in turn, have been held responsible for exciting this disease. Apart from the relief afforded by salicylates, the treatment of the heart and joint lesions is still unsatisfactory, and it is not possible at present to prevent the chronic invalidism resulting from the involvement of the heart or of the joints.

That chronic inflammation with its attendant fibrosis can be resolved without operative interference is not generally accepted. On this basis, therefore, subacute and chronic rheumatism doom individuals to life-long handicap. However, there is some evidence to show that excess fibrous tissue in arteries and even in organs may resolve spontaneously under favorable conditions. We have seen a sclerotic partially calcified uterine blood vessel soften during pregnancy. Similar reactions have also been noticed in the ovary. Despite the highly specialized nature of these vessels, we are satisfied that the sclerosis yields sufficiently to a proper stimulus to allow the vessels to cope with the great functional needs imposed by a pregnant uterus. Similarly Cameron and Karunaratne[3] have indicated in their experiments that the fibrosis induced in the liver by chronic carbon tetrachloride poisoning, at a certain stage, is reversible. More recently, Bogomolets[2] by means of his, anticytotoxic sera claimsto resolve those fibrotic reactions characteristic of aging. These isolated observations reveal that by a correct approach it may not be impossible to facilitate the absorption of the fibrous tissue characteristic of the lesions of chronic rheumatism and arteriosclerosis.

The present traditional approach to disease, which has thrown much light on many pathological processes, has thus far proved inadequate in solving a variety of puzzling and crippling diseases, like rheumatism. Speransky,[5,8] one of Pavlov's students, has emphasized the rôle of the nervous system in the causation of disease and in determining many manifestations not otherwise satisfactorily explained. By accepting as a working hypothesis that disease is not merely an expression of deranged normal function but indeed is an entirely new phenomenon having no counterpart in health, he was led to adopt

* This study of a unique therapeutic approach to "Rheumatism" reached our office after being 8 months in transit. The distance from Johannesburg precludes further correspondence before publication. The assessment of an unusual new therapy in arthritic conditions, particularly when it is without apparent fundamental rationale, is difficult. Of this the authors are well aware, for they have approached their subject objectively. They recognize the possibility that such factors as other medicaments used, autosuggestion, widely varying concepts of "rheumatism" in different countries and so on, might easily cloud their judgments of the effects of their specific therapy. Nevertheless, they have placed their observations on record in the hope that others may add further data to the problem before final opinion is rendered —The Editors.

unorthodox procedures in studying pathological processes and in fashioning entirely new therapeutic methods. One method introduced by Speransky into clinical medicine is "spinal pumping." This he has applied in the treatment of 100 patients with polyarthritic rheumatism. Of these, 52 were treated during their first acute attack of rheumatic fever; 36 (70%) recovered completely; 33 had suffered more than one attack and of these 23 (73%) had no further attacks, and of 15 cases with chronic arthritis recovery was noted in 4 cases, improvement in 9, while 2 remained unchanged.

Comparing these results with those following the treatment of 127 cases of rheumatic fever with salicylates alone, Speransky remarks that, of the latter group, only 61 (48%) recovered completely.

Speransky moreover draws attention to the fact that "the first signs of objective and subjective improvement were noted within 10 hours after pumping in 27% of all cases and within 48 hours in more than 80%. Within 48 hours, objective changes had completely disappeared in 24 cases and in 18 of these there were no subjective complaints."

We have for some time devoted our attention to the problem of the rôle of the nervous system in disease, and in view of the dramatic changes observed by Speransky in cases of rheumatic fever treated by spinal pumping, we decided to examine the efficacy of his methods in the treatment of this common and devastating disease.

Spinal pumping seemed to many of the clinicians in Johannesburg such an unorthodox form of treatment, that we experienced considerable difficulty in obtaining cases of acute rheumatism with early involvement of the heart despite the fact that our experience indicated that at this early stage, rheumatism might respond most satisfactorily. We were therefore allowed to perform spinal pumping only on those cases which were resistant to all other forms of treatment. The results obtained were so remarkable that we feel obliged to report our findings, especially as at present there is little likelihood of our being able to test out this method on a large series of cases under controlled conditions. We realize that 70 cases of the type available to us are obviously insufficient to allow of a proper assessment of the value of spinal pumping, but in view of some of the dramatic effects obtained and in view of the limited numbers of cases available in Johannesburg, we think that the publication of this report might perhaps encourage other workers in more favorable circumstances to test out on a large scale a therapeutic measure which, in our opinion, has the possibility of bringing relief to many individuals suffering from rheumatism.

Material. This report is based on the study of 70 patients suffering from acute, subacute or chronic forms of rheumatism with joint involvement. All the patients, with 3 exceptions, were adults.

Twelve of the 70 patients were treated during their first attack of acute rheumatic fever. In all patients, several of the large joints were swollen and exquisitely painful.

The 36 patients with subacute arthritis all complained of swelling, pain and limitation of movement in large and small joints, especially the knees, wrists, elbow, shoulder, metacarpophalangeal and interphalangeal articulations of varying duration. In 32 of the patients, the arthritis had started with an acute attack of rheumatic fever, associated with pyrexia, acutely swollen, painful large joints. The acute attack resolved slowly and then only partially. Residual lesions of varying severity were localized chiefly in several large joints as well as the small joints of the hands. Patients were rarely free from swelling and pain and the movements of the affected joints were limited. The majority of these subjects had already been treated in the usual way with typhoid or protein shock, diathermy, gold, aluminum or bee venom injections, diet and even hyperthermia and other forms of physiotherapy. It was only after these methods had brought no relief that spinal pumping was attempted. The arthritis in the remaining 4 subjects in this group, could, in our opinion, be regarded as entirely different

from that commonly seen in rheumatism. In these 4 cases the disease started soon after a severe emotional shock. The onset was not acute nor was it associated with swelling, pain or pyrexia. On the contrary, there was a gradual limitation of movement followed later by pain, deformity and contracture. The response to spinal pumping too, indicated a different etiology.

The 22 chronic arthritics in the main were over the age of 40 years, with a history extending over 3 or more years. The deformities were severe and radiologic examination revealed gross bony changes in and around the affected joints. In addition to the grossly distorted joints, 12 of the patients gave a history of recent swelling of joints in which only mild bony changes were visible radiologically. In most instances there were other signs usually found in chronic rheumatism, namely, trophic changes in the skin and muscles around the affected joints, thenar and hypothenar erythema, and vascular spiders.

Methods. In all but 2 instances, 10 gm. of sodium salicylate in divided doses were administered orally or rectally 24 hours before pumping and for 24 to 48 hours afterwards. In view of the effects on the bleeding tendency produced by large doses of salicylates,[7] the prothrombin index was performed according to the method described by Stein[9] on all those subjects taking salicylate for more than 3 days prior to the pumping.

The spinal pumping was performed in accordance with the method described by Speransky. However, as the technique of this procedure is described so briefly in his book and as we believe we have been able to overcome many minor difficulties, we offer no excuse for describing this method in detail.

Procedure. After inducing local skin anesthesia with 2% procaine, a lumbar puncture is performed with the patient in the left or right lateral position. Where the stiff joints made this position inconvenient, the sitting position was adopted.

A thin lumbar puncture needle with a very short bevel is ideal for this purpose, especially as it is essential to perform the lumbar puncture in such a way that the needle point lies *just* within the subdural space. After inserting the needle and when the cerebrospinal fluid flows freely, a good 10 cc. syringe (preferably all glass) is firmly attached.

The actual "pumping" consists in withdrawing into the barrel of the syringe 10 cc. of cerebrospinal fluid and re-introducing it into the subdural space. This procedure must be carried out so slowly that it takes at least ¾ to 1 minute to withdraw the fluid, and the same time to push it back. On no account should the fluid be forcibly extracted or hurriedly forced back. The fluid should flow so easily that only gentle traction on the plunger with one finger should be sufficient to cause continuous flow. When the pumping is executed with the patient in the sitting position, the pressure of the cerebrospinal fluid alone should be sufficient to push out the plunger of an all-glass syringe and no actual suction should be applied. In our cases 10 cc. of cerebrospinal fluid (only 6 cc. in children) were withdrawn and reintroduced 20 times. At the completion of the spinal pumping, 10 cc. of fluid were removed and discarded. The procedure should occupy 40 to 50 minutes.

If the fluid does not flow easily, it sometimes helps to introduce the needle a little deeper or withdraw it slightly by gentle traction. If the fluid still fails to flow freely the patient is gently raised into a sitting position. Usually, these procedures produce the desired effect, but sometimes it may be necessary to withdraw the needle completely and then re-introduce it through another intervertebral space.

Occasionally, when the fluid is being withdrawn, the patient complains of a sudden sharp twinge of pain referred down one or the other leg or to the coccyx. This sensation is consistently described as being "just like an electric shock." It passes off as quickly as it appears. This twinge invariably occurs when fluid is being withdrawn too rapidly. The operator experiences a definite impulse as if something has floated up against the needle point and, moreover, the flow of fluid is momentarily interrupted. It is probable that this sensation is caused by the sucking up against the needle of one of the nerves of the filum terminale. When this occurs it is advisable to re-inject 1 or 2 cc. of fluid and to pause for 10 to 15 seconds before proceeding with the extraction of the fluid; the needle should then be withdrawn slightly before attempting the next cycle.

Since this delicate manipulation may take

an hour to complete the operator should be comfortably seated.

Discussion. It is generally recognized that the swollen tender joints in acute rheumatic fever can disappear spontaneously in a most unpredictable fashion. It would seem, therefore, that but little reliance could be placed on the results obtained by spinal pumping. However, it is also known that, in many cases, despite all known forms of therapy over several weeks, the disease does not improve. It is our opinion that spinal pumping will hasten the relief in acute forms of rheumatic fever, especially as in this study, only cases were available in which other forms of therapy brought no relief and where the sedimentation rate remained persistently raised.

The assessment of improvement in the non-chronic cases was based on the general clinical condition, the temperature, pulse rate, sedimentation rate (1 hour Wintrobe method corrected for anemia), the diminution of swelling and pain, an increased range of movement of the affected limbs, together with any subjective information volunteered by the patient. In subacute cases, in addition, special attention was given to the peripheral circulation as expressed by the color and temperature of the fingers and toes and the atrophic, smooth, shiny skin over previously affected joints. The general improvement of the clinical condition as reflected by a gain in weight is sometimes an additional indicator of a remission in this disease.

The assessment of improvement in chronic cases is always extremely difficult, especially as such patients frequently have remarkable faith in any "new" treatment. They are usually mentally active and extremely eager to recover from their very crippling disease. Consequently, objective signs were relied upon and improvement was regarded as having taken place only in those patients in whom a very appreciable increase in the movement of one or more joints was noted, as well as a gain in weight, an increased appetite and restful sleep.

Regarding the terminology used in the assessment of the responses to spinal pumping, those patients in whom there were no objective signs of active disease were regarded as recovered. Those in whom there was a marked recovery of joint function in one or more joints, together with an associated drop in the sedimentation rate and a distinct amelioration in other signs and symptoms of the disease, were regarded as improved. The term "unchanged" is applied in this study to those cases in which there was no objective evidence of recovery.

Results. *Effects on the Joints.* The results in 70 cases are summarized in Table 1. Six of the 48 cases of acute and subacute arthritis showed no objective evidence of improvement. The remainder, however, were distinctly improved, although the rate of recovery varied in different patients. In 10% of those improved, the effects were noticeable immediately after the pumping was completed, as expressed by an increased movement and diminution of pain in the affected joints. The majority of patients (70%) was relieved within 12 to 36 hours, and another 20% responded at the end of 72 hours. The remaining cases showed a steady improvement which was maximal at the end of 2 to 3 weeks.

Although spinal pumping was followed by recovery of joints in which there were obvious pathologic changes in the bone, nevertheless, in acute attacks associated with pain and swelling superimposed upon the chronic lesion, this treatment curtailed the acute attack and apparently arrested the progress of the disease. For this reason, no recoveries among chronic cases are found in Table 1, but 12 of the 22 cases were considerably relieved. In general, therefore, the results obtained in this series of cases confirms those recorded by Speransky.

Relapses. Unfortunately, in Johannesburg, there is no organized service for the proper treatment and extended surveillance of patients suffering from the various manifestations of rheumatic fever. As a

consequence, it was possible to follow out the end results of spinal pumping only in 29 cases, for periods varying from 2 weeks to 18 months.

Eleven acute and subacute cases were under observation for 2 to 6 weeks. Of the 4 acute arthritics, 1 has remained well for the last 18 months while 3 relapsed within 7 to 16 days. It must be stated, however, that the relapse was only partial and after a second pumping these 3 patients have maintained good health for the past 8 to 18 months.

3 months later the patient relapsed again and spinal pumping was then without effect. This is the only patient in this series where a repeated spinal pumping failed to produce an effect after the first and second pumping had proved successful.

Of the 18 cases of acute, subacute and chronic arthritis who responded to spinal pumping and who have been under observation for 4 to 18 months, the disease has progressed in only 1 instance, and this in a patient with chronic arthritis.

TABLE 1.—CONDITION FOLLOWING TREATMENT

Type of arthritis	No. of cases	Responses			
		Recovered	Improved	Relapses	Unchanged
Acute	12	10	..	3	2
Subacute	36	28	4	3	4
Chronic	22	..	12	2	10
Total	70	38	16	8	16

Four of the 8 subacute cases experienced a partial relapse within 6 weeks, but after the second pumping 3 have remained well up to the present (8 to 18 months), while the fourth was pumped a third time and has suffered no further setback over the last 16 months. In addition to these, 8 other patients suffering from subacute arthritis who left the hospital within a few days after the first pumping have been under observation for 6 to 18 months. Two relapsed partially and the 1 who submitted to a second pumping has remained well for the past 5 months. The other patient regarded the degree of discomfort as so slight in comparison with the initial lesions that he did not feel inclined to have a second treatment unless the residual lesion progressed, which it has not done during the 4 month period of observation.

In the chronic cases, 6 were followed over 4 to 18 months. Two of these improved for a short period of time and then deteriorated. One of these patients showed a remarkable improvement during the first 6 months. Thereafter, both ankles became swollen and a spinal pumping was again performed with good result. However,

On the basis of this small group in which follow-up studies were possible, it would appear that: first, a single spinal pumping can be followed by lasting beneficial effects; second, when a relapse occurs it is usually not as severe as the initial attack; and, third, if spinal pumping induces salutary effects on 1 occasion then a second or even a third pumping is indicated in the presence of refractory joints or if a partial relapse occurs. Moreover, there is suggestive evidence that spinal pumping may arrest the progress of subacute or chronic arthritis.

Effects on Other Systems. *Peripheral Vascular System.* One of the remarkable features of spinal pumping, not mentioned by Speransky, is the profound effect on the peripheral vascular mechanism. This is expressed by severe sweating, a rise in skin temperature and a marked dilatation of the capillaries with noticeable pulsation, especially in the fundus oculi. Many of these reactions may occur after the tenth or twelfth cycle of pumping, but in the majority of patients they appear within a few hours after the treatment.

The extent of the perspiration varies

considerably. In some the skin over the whole of the body becomes clammy, whereas in others the patient may actually soak the bedclothes. This reaction may continue for as long as 48 hours.

During, or soon after the pumping, the extremities too, become appreciably warm or even hot. During the early stages of this study it was not possible to obtain accurate records of this phenomenon; however, in a few cases, the records of the skin temperature demonstrated that the temperature could be elevated by as much as 20° F. above the initial level, and that this full dilatation of the peripheral vessels could be sustained for 6 hours. The degree and duration of the dilatation of the peripheral vessels is much greater than is usually achieved after sympathetic blocks. Even the patients were conscious of this increase in warmth and they themselves frequently remarked that they had not experienced such warm extremities for years.

This effect was maintained for many months in patients who responded favorably, and even those whose joints had shown no improvement were glad of the relief from discomfiture of cold hands and feet. Apart from these visible effects on the peripheral blood vessels inspection of the retina has revealed marked pulsation of both arteries and veins immediately after pumping. In 1 patient suffering from weekly attacks of severe migraine, the spinal pumping precipitated a violent attack which persisted for 2 days. Since then, however, the patient has not complained of migraine for the past 12 months.

Since spinal pumping has widespread influence on the vascular mechanism there seems little doubt that these reactions are manifestations of a profound disturbance in the central nervous system, simulating the clinical picture of concussion. This similarity is further emphasized by the frequent interference with the heat regulating mechanism. In 20 cases of subacute arthritis with normal temperatures, spinal pumping resulted within 8 to 18 hours in an elevation of the temperature from 1° to 5°, lasting for 4 to 12 hours. In 2 patients there was a remittent pyrexia for 2 days, but this settled without any specific treatment. These alterations in the body temperature after pumping are in no way related to the nature and extent of improvement in the affected joints and the pyrexia itself cannot be considered as the important factor in the relief in the joints, as is said to be the case in shock therapy. This is supported by the fact that less than a third of the patients experienced pyrexia, and, moreover, the same patient may, on 1 occasion, show a marked rise in temperature and after a second pumping there may be no reaction of this nature. Similarly, in other subjects at the first pumping, there was no rise in temperature, but, on a subsequent occasion, it was raised. It is not possible to predict when a rise in temperature will occur or to correlate such instabilities of the temperature with any subjective or objective improvement.

Spinal pumping has a totally different effect where the temperature is elevated in acute attacks of rheumatic fever, especially where the temperature has remained elevated for several weeks, despite liberal doses of salicylate. In 10 such instances, after the spinal pumping, the temperature dropped by crisis.

There were a number of incidental beneficial effects following pumping which might be related to the disturbance in the peripheral vascular mechanism. Of special interest is the disappearance in 7 cases of long-standing skin rashes. In 6 of these the rash was of the sudaminal variety and, despite the profuse sweating which persisted for several days after the pumping, these rashes, generally thought to be caused directly by the sweating, cleared within 24 hours. In 1 instance, multiform acneform pustules on the face, abdomen and especially the back, were absorbed within 12 hours and could be recognized only as dull reddish-brown pigmented plaques.

The improvement in the joint lesions was always reflected by a diminution in

the sedimentation rate. Frequently the sedimentation rate increased during the first week, and, thereafter, settled rapidly to normal. Usually, in those with persistently raised sedimentation rates who responded to pumping, the sedimentation rate returned to normal within 2 weeks, although it had previously remained elevated, despite the administration of massive doses of salicylates.

This favorable effect on the sedimentation rate was associated with a noticeable improvement in the general condition of the patient. The weight increased, the appetite was regained and sleep became restful. The protocols of 2 cases, 1 with subacute arthritis and 1 with acute rheumatic fever, are included here to indicate the nature of the responses observed.

Case Abstracts. CASE 1. *Subacute Rheumatoid Arthritis.* Male, aged 33, with extensive bilateral affection of knees, ankles, shoulders, wrists and hands. All these joints were swollen, extremely painful and movement was so limited that the patient had to be fed. The patient had been in the ward for 4 months and had been treated with salicylates, protein shock, gold, arthritin, aluminum acetate, bee venom and physiotherapy, without any result. On the day of pumping (May 6, 1943), he could not flex his fingers, wrists, elbows or knees, the right arm could not be abducted at all and the left could only be abducted 15 to 20°. The patient stated that he had such severe pains in all his joints that he could not sleep. Sedimentation rate (corrected for anemia, 1 hour Wintrobe) 52 mm. A total of 120 gr. of sodium salicylate were administered in 4 hourly doses for 24 hours before, and for 24 hours after, pumping.

Pumped 15 times at 6 P.M., May 6, 1943. On the morning of May 7th the patient was very bright; he slept well and could now flex hands, fingers and knees. The pain had been considerably alleviated and the swelling of these joints had subsided. On May 8th he walked for the first time since entering hospital; but, on walking, complained of pain in the right ankle. Patient continued to be well for the following 3 weeks and then the right elbow again became swollen. Salicylates were again administered for 24 hours and the patient was pumped on May 28th. Full movement recovered 12 hours later. Joints remained well and patient's general condition improved remarkably. On June 4th sedimentation rate (corrected) was 22 mm. Patient was detained until June 23rd in excellent condition. There was some residual tenderness of the third and fourth metacarpophalangeal joints of the right hand. Sedimentation rate on June 23rd was 10 mm. On August 14th patient was seen again and was still well.

CASE 2. *Acute Rheumatic Fever.* A 23 year old female was admitted with acute rheumatic fever and arthritis affecting chiefly the right hand, the thumb and wrist, left shoulder, right knee and ankle. She was treated with local applications and 2 gm. of sodium salicylate 4 hourly for 2 weeks with slight improvement. However, on July 27, 1943 the left ankle and left knee became swollen and the temperature was still elevated to 101°. Sedimentation rate (corrected) was 42 mm. on July 26th. Spinal pumping was performed on July 29th at 4.30 P.M. During the night she developed a severe frontal headache. At 11 A.M. on July 30th the bandages were removed and patient, to her surprise, could flex her joints completely. The swelling of the left ankle and knee had disappeared and that of the right knee and ankle had subsided considerably. The left shoulder was still slightly tender to pressure but the movement had improved considerably. The temperature was now normal and remained so until the patient was discharged. On August 2d the patient got up and walked around without any pains at all. Grip of right hand now normal. Sedimentation rate on August 9th was 16 mm. Patient reported back on October 20, 1943 and June 16, 1944 and stated that she had been well and indulged in all forms of exercise. There were no objective signs of arthritis in any of the affected joints on June 16, 1944.

Miscellaneous Effects. Several untoward reactions following spinal pumping noticed by us were not mentioned by Speransky. Severe headache in 20 instances and vomiting in 10 were the commonest complications. At first, such headaches were regarded as due to low pressure following the removal of the 10 cc. of fluid.

Actually, the pressure very often rose steadily during the pumping and, at the end of the 20th injection of the fluid, it was frequently 100 to 150 mm. higher than at the outset. With the extraction of 10 cc. at the end of the pumping the pressure returned to normal. It is likely, however, that, after the initial generalized vasomotor disturbance, the pressure may fall and so evoke the low-pressure headache, which as a rule appears within 4 to 6 hours after pumping. There is, of course, the possibility that the pumping may stimulate an increased secretion of cerebrospinal fluid and the resulting headache would then be due to increased intracranial pressure. Although no observations were made on the cerebrospinal fluid pressure during these headaches, from the responses to fluids, drugs and posture it would appear that the headaches may be due in some patients to low, and in others, to increased pressure. That some form of cerebral irritation is induced is evident from the vomiting as well as photophobia and even pyrexia which may sometimes be associated with severe headache. It must be remembered, however, that salicylates *per se* may cause severe vomiting through its effects on the stomach or liver or even *via* the central nervous system. Relief from the headache may be satisfactorily provided by judicious administration of barbiturates and codein or, in some instances, of caffein intravenously.

The fact that the vascular mechanism in the brain is apparently disturbed profoundly by spinal pumping is a matter of some importance, especially as it may determine the type of case suitable for pumping. Speransky draws attention to some of his experimental findings that, if in dogs *all* the cerebrospinal fluid is repeatedly withdrawn and re-introduced, then the fluid may become blood-stained and acute hemorrhages occur in the brain itself. Red blood cells were not identified microscopically in the cerebrospinal fluid removed from 20 cases after pumping. In the remaining cases the fluid was macroscopically normal. However, in view of the profound cerebral vasodilation which appears to be a notable reaction to pumping it is likely that, in the presence of hypertension or cerebral vascular disease, the increased strain on the arterioles may result in a cerebral hemorrhage. This possibility is suggested by the occurrence of multiple cerebral hemorrhages in a patient after spinal pumping. A summary of the clinical history and autopsy findings in this patient is as follows:

Clinical Summary. The patient, a female aged 45, was admitted to hospital with a typical attack of rheumatic fever which developed 3 weeks after a Pott's fracture of the left leg. All the large joints were swollen and exquisitely painful. The blood pressure was 168°110. The temperature remained elevated for 17 days, despite the continued administration of 120 to 180 gr. of sodium salicylate throughout this period. The joints were extremely painful throughout, and the pain could only be alleviated by repeated administration of morphine. In view of the hypertension and our knowledge that pumping results in dilatation of cerebral vessels it was thought unwise to perform a spinal pumping. However, in view of the fact that the patient was not responding to treatment, as well as the absence of any record by Speransky of any untoward events following this procedure in man, we finally decided to perform spinal pumping. This was done even more slowly than usual.

The temperature came down by crisis within 16 hours of pumping and the patient was extremely pleased with the relief from the severe joint pains which accompanied the diminution in the swelling and the increased movement. The patient complained of a severe headache for the next 14 hours, which was considerably relieved by 2 tablets of A.P. Cod., 4 hourly. The temperature during this period remained normal and continued thus for the next 3 weeks. Whereas the knees, right ankle, wrists, shoulders and right elbow returned to normal within 48 hours of the pumping, the left elbow, although it had improved considerably, remained slightly swollen and painful. During the next 2 weeks the joints became progressively worse and the pain returned to the left shoulder. In view of the excellent response obtained with the first pumping

and the absence of any unusual reactions, it was decided to repeat the treatment. Salicylate therapy, which was discontinued 48 hours after the first pumping was again instituted and 48 hours later a second pumping was performed. This time 10 cc. of fluid were extracted and reinjected only 10 times. Within 16 hours the patient had recovered full movement in the left elbow and shoulder and the joints appeared objectively normal. The patient again complained of headache but was otherwise bright and very pleased with the result. Twenty hours after the pumping the temperature rose to 101° but the patient, although flushed, still felt perfectly happy. This temperature was remittent for the next 48 hours and on the 3d day after pumping the patient became drowsy and giddy and during the next 12 hours became stuporous and then comatose. Lumbar puncture at this time revealed a negative pressure of 15 mm. The breathing was now stertorous, the pulse was rapid and bounding and the temperature had risen to 104°. There were no localizing signs, the pupils remained equal and dilated until death. Blood pressure at this time was 180/110. The patient never recovered from coma. Respiration failed at 10 P.M. of the 3d day after the second pumping and artificial respiration was instituted, together with repeated injections of picrotoxin and adrenalin. The circulation was maintained actively until 2 A.M. the following morning when it slowly failed.

Autopsy: This revealed multiple small cerebral hemorrhages in the occipital and frontal lobes, together with numerous fine petechial hemorrhages scattered throughout the brain substance. The basal cerebral vessels showed no signs of degenerative disease. However, the myocardium was thickened, due to hypertrophic changes. Death was due to cerebral hemorrhage.

The strange mode of onset of the hemorrhages and the unusual sites, as well as the fact that these became clinically recognizable for the first time only 3 days after the second spinal pumping, made it extremely difficult to assess the part played by the pumping and the hypertension in the production of the cerebral catastrophe. It was considered that the hypertension, together with the increased cerebral vascularity which we think was to be produced by the pumping, might have resulted in the bursting of the weakened vessels in the frontal and occipital regions.

However, Ashworth and McKemie recently reported[1] 2 patients who died from multiple cerebral hemorrhage following salicylate therapy alone. The probability presents itself, therefore, that death in our single case was in no way attributable to pumping but was rather the result of the capillary damage and hypoprothrombinemia produced by salicylate poisoning.

Since this accident, we now regard any signs of vascular disease as a contraindication for spinal pumping; but it still remains to be firmly established whether this is justified or not.

Indications for Spinal Pumping. On the basis of our experiences as well as of those from the limited records available to us in Speransky's book,[8] we recommend spinal pumping under the following conditions, in order of importance:

1. In patients suffering from a first attack of acute rheumatic fever who have not responded to treatment with 90 to 180 gr. of sodium salicylate daily for 2 to 3 weeks.

2. In subacute arthritis following an attack of acute rheumatic fever where the disease has been present for less than 18 months. Early bony changes, while not a contraindication to this form of therapy, militate against the excellent responses observed in subjects without any involvement of the bones.

3. In chronic arthritis where new joints previously unaffected have recently become involved.

4. In chronic arthritis in which the cold extremities are a source of great discomfort.

Contraindications to Spinal Pumping. 1. Until disproved, the presence of any form of vascular disease in which the cerebral vessels may be implicated must be regarded as a contraindication to pumping.

2. Complete destruction of joints.

3. A low prothrombin index, due either

to prolonged salicylate therapy, or to the hepatic disease that is so frequently present in chronic arthritis.

In 3 cases of acute gonococcal arthritis spinal pumping was ineffective. Moreover, spinal pumping is also ineffective in those forms of arthritis in which swelling of the joints is apparently secondary to intra-articular disease. In our opinion, this arthritis is unrelated to rheumatic fever and usually commences as a gradual contraction of the joints following a severe emotional storm.

Comment. The nervous system is not generally considered to play more than a subsidiary part in inflammatory processes. Even where the nervous component of an inflammatory process is admitted it is regarded as an auxiliary factor capable only of exerting an indirect influence on the course of the inflammation and not on its quality. By a series of brilliant experiments, Speransky arrived at the opinion that, not only does the nervous system play more than a minor part in inflammation, but the course, if not the genesis, of the inflammation is directly determined by the nervous system.

When rheumatic fever expresses itself in the form of chorea it is generally believed that the nervous system in such instances is involved in the same way as any other part of the body. The peculiar reactions seen in chorea are regarded as a manifestation of a functional derangement resulting from a nervous form of rheumatism. However, when other parts of the body are affected by this strange disease, it is not generally appreciated that the nervous system is still implicated. Despite the fact that rheumatism is invariably associated with a generalized derangement of bodily function, as expressed by the pyrexia, irritability, vasomotor disturbances and metabolic changes, when it appears to be localized in the heart or the joints, attention is directed to the affected parts and the therapy is designed accordingly. The rôle of the nervous system in these circumstances is, as a rule, completely overlooked, and no attempt is made to attack the disease by concentrating on this aspect of the organism.

There is scattered evidence that the nervous system plays a considerable rôle in the pathogenesis of rheumatic fever and rheumatoid arthritis, even when it is not so grossly involved as in chorea.[6] This is illustrated especially by the muscular reactions and trophic changes which accompany rheumatoid arthritis. The atrophy of the muscles in this disease is usually attributed to disuse of the affected joints. However, the rapidity and extent of the wasting is out of proportion to the duration of the disease. Such rapid muscular atrophy is characteristic of nerve lesions. The fibrillation so commonly observed in the muscles around the affected joints in arthritis also suggests the implication of the nervous system and the typical trophic changes in the skin in rheumatism are similar to those usually described after nerve lesions.

That injury to the nervous system may be attended by metabolic disturbances is well known. However, it is not generally appreciated that the introduction of toxins into the nervous system can excite reactions in remotely removed organs similar to those encountered after the administration of the same toxins intravenously.[5] Speransky has produced a type of carditis by the intrathecal administration of small doses of diphtheria toxin in a passively immunized animal, indistinguishable from that following severe diphtheria intoxication.[5,8] It seems very likely that the carditis and arthritis as well as the other manifestations of rheumatic fever may in large measure result from a widespread involvement of the nervous system.

While relief must be provided to the parts of the body obviously affected by an attack of rheumatic fever, if lasting and effective treatment is desired, attention must be directed also, in our opinion, to the nervous system. Irrespective of its mode of action, there can be little doubt that spinal pumping produces some interference with the nervous mechanism and

can, and does lead to spectacular responses in the various forms of rheumatism resistant to the usual forms of therapy.

Since salicylates have been used in conjunction with pumping it might be argued that spinal pumping has so affected the blood brain barrier as to allow the increased penetration of this drug into the cerebrospinal fluid. This was the view which Speransky originally propounded, but later it was rejected when more experimental evidence was forthcoming. We have not been able to find any significant increase in the salicylate content of the cerebrospinal fluid immediately after, or even 24 hours after, spinal pumping. Moreover, the bromide test of the blood brain barrier which was performed in 6 cases who were pumped, failed to demonstrate an increased bromide content of the cerebrospinal fluid after pumping. The final proof that salicylates are not alone responsible for improvement is indicated by the fact that in 2 cases the response was no less effective *without* salicylates. These findings add further support to Speransky's hypothesis that spinal pumping acts directly on the nervous system.

Although, in the present stage of our knowledge, it is not possible to provide a scientifically plausible explanation for the mode of action of spinal pumping, nevertheless, the fact that, after pumping, a joint immobilized for many months is capable, within a few hours, of assuming full function is remarkable and has extremely important implications. The present orientation towards the factors responsible for immobilization of the joints in acute and subacute rheumatoid arthritis require to be reviewed in the light of these findings. It is evident that if the joints were fixed by fibrous tissue after a long period of immobility, it should be scarcely possible to induce movement within a few hours. The present methods adopted by orthopedic surgeons in manipulating joint contractures resulting from rheumatism are obviously not directed by any rational understanding of the pathologic processes in and around these diseased joints.

Although the rapid recovery of movement within a few hours of pumping cannot be attributable to a loosening of fibrous bands, nevertheless, we have evidence that the fibrous tissue in rheumatism can be absorbed, not only from the periarticular regions, but also from other parts of the body. We have actually seen subcutaneous nodules disappear within 24 to 48 hours after pumping.

If fibrous tissue can disappear, as it does, from some parts of the body, then there is every reason to suppose that, at certain stages of the disease, spinal pumping may lead to the absorption of fibrous nodules from the heart and even from the valves. Speransky has drawn attention to the disappearance of murmurs in rheumatic fever after pumping. Unfortunately, up to the present we were only allowed access to such patients as would not respond to other forms of therapy. From our experience we are sufficiently optimistic to suggest that the most dramatic effects can be anticipated in the acute and subacute forms of rheumatism.

At present, when the heart is involved, treatment is palliative as there are no known methods of resolving or even arresting the progress of rheumatic pancarditis. While we do not, at this stage, recommend the universal application of this simple procedure, we do feel that a thorough investigation of spinal pumping in all forms of acute and subacute rheumatism under controlled conditions may prove to be invaluable in our attack on the devastating effects of rheumatism.

Finally in view of the effects of spinal pumping on the peripheral vascular system already described, it seems that this method may also be used to advantage in those diseases where it is desirable to excite a marked and prolonged dilatation.

Spinal pumping has proved effective in a variety of seemingly unrelated diseases.[8] The fact that many of these diseases respond to a single non-specific method of therapy lends support to Speransky's con-

tention that, however divergent the pathologic processes in these diseases may appear to be, there is one feature common to all, namely, that the nervous system is significantly implicated to a greater or lesser extent. Speransky is responsible for redirecting our attention to this important part of the body and for providing a reorientation in our understanding and attack on many diseases which, hitherto, have proved refractory to our present methods of therapy based on the orthodox concepts of disease.

Summary. Using spinal pumping in the treatment of 70 cases of acute, subacute and chronic rheumatism with arthritis, it was shown that in 38 of 48 cases of acute and subacute arthritis all objective and subjective signs of the disease disappeared, and 12 of 22 chronic cases were improved. In many instances, full function was regained within 4 days. These observations tend to confirm those recorded by Speransky in 100 cases with various forms of rheumatic polyarthritis.

Spinal pumping has a profound effect on the peripheral blood vessels leading to a prolonged vasodilatation.

Conclusions. It is suggested that, with due regard for the difficulties of evaluation, it appears that spinal pumping may arrest the progress of rheumatic fever, especially in the acute and subacute stages, and may be of value in the early stages of rheumatic pancarditis.

Since this study tends to confirm Speransky's observations on the value of spinal pumping in the treatment of the various manifestations of rheumatic fever, and in view of the significant changes induced in the peripheral vascular system by this form of therapy, we strongly recommend that this method be given further trials on a larger series of cases under controlled conditions.

We wish to acknowledge our great indebtedness to Prof. Raymond A. Dart for his interest and encouragement. Our thanks are due to Dr. L. I. Braun and Dr. N. V. Storr as well as Drs. B. Cohen, J. J. de Waal, T. Schneider, A. Koenig, S. Heiman and H. L. Heimann for allowing us access to their clinical material.

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THE CHANGE IN PLASMA VOLUME AND BODY WEIGHT IN NORMAL SUBJECTS AFTER A LOW SALT DIET, AMMONIUM CHLORIDE AND MERCUPURIN*

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Recent work[11,12,13] has indicated that the plasma volume in normal subjects may fluctuate considerably with small changes in the fluid content of the body associated with the administration of sodium salts or the use of diuretics. Similar and more extensive changes in animals have also demonstrated the fact that the plasma volume is to a considerable extent dependent on the extracellular fluid volume.[14,16]

Decreases in the fluid content of the body, produced by means of diuretics such as ammonium chloride or mercupurin, is the accepted treatment of edematous subjects. Though there has been considerable investigation of the biochemical action of ammonium chloride,[3,5,6,9,10,17] there is little information available concerning the diuretic effect that might be expected in the non-edematous hospital patient on an unrestricted diet. In general, the same difficulty is encountered concerning the action of mercurial diuretics on normal subjects, though Blumgart *et al.*[2] did a careful study on a few subjects. The combination of acid salts with mercurial diuretics to enhance the diuretic action of both drugs has been extensively studied,[4,8,9,15] but again little information is available concerning the effect of the combination of these drugs on the normal subject.

Such diuretics may serve as a means of producing an experimental type of dehydration in normal subjects. They have been used in this study to demonstrate the changes in plasma volume associated with the loss of body fluid.

This report deals with the changes in body weight, plasma volume, serum protein concentration, and total circulating protein of normal subjects following the combined use of a low salt diet, ammonium chloride, and mercupurin. The diuretic action of the low salt diet and ammonium chloride alone and of mercupurin alone is compared to the effect of the combination of both drugs in the normal subject.

Methods and Materials. The effect of mercupurin alone on the plasma volume and body weight of 10 normal subjects was previously studied by determining these measurements before and 24 hours after intravenous injection of 2 cc. of the drug. The results have been described in detail elsewhere,[13] and the change in body weight and plasma volume are included here for the purpose of comparison. The rôle of a low salt diet and ammonium chloride on plasma volume and body weight in 15 normal subjects also has been described.[11] The 9 normal subjects reported here were selected from the above group largely because of their availability and willingness to continue the study. After control determinations, they were placed at bed rest and consumed a low salt diet (about 2.5 gm.) adjusted in calories to 40% above the estimated basal

* Supported by grants from the Board of Governors of the Horace H. Rackham School for Graduate Studies, and the Upjohn Company.

TABLE 1.—CHANGES IN PLASMA VOLUME, HEMATOCRIT, SERUM PROTEIN CONCENTRATION, TOTAL CIRCULATING PROTEIN AND BODY WEIGHT

	1	2	3	4	5	6	7	8	9
CONTROL DETERMINATIONS									
Plasma vol. (cc.)	2800	3090	2600	3030	3030	2560	3180	2730	3210
Hematocrit	35.7	46.2	42.0	41.2	45.9	39.1	44.5	44.9	49.3
Total protein concentration (gm. per 100 cc.)	7.13	6.82	6.16	7.79	5.85	7.06	7.20	7.06	
Total circulating protein (gm.)	199	211	160	236	177	181	229	193	
Body weight (kg.)	42.0	80.0	44.0	58.5	43.3	53.3	52.0	61.2	70.1
CHANGE FROM CONTROL DETERMINATIONS AFTER A LOW SALT DIET AND AMMONIUM CHLORIDE									
Change in plasma vol. with NH_4Cl from control determination	−400	−210	−60	−430	−1060	−670	−10	−160	−630
Mean: −403 St. dev.: 321 St. error: 114									
% change in hematocrit	−7.5	−4.1	−9.7	−7.0	+1.1	−2.0	−8.3	−6.7	+22.1
Mean: −2.45 St. dev.: 9.26 St. error: 3.27									
% change in serum protein concentration	+1.8	+14.3	+8.5	−11.5	+19.6	0	−5.8	−2.9	
Mean: +3 St. dev.: 9.8 St. error: 3.69									
Change in body weight (kg.)	−1.6	−2.9	−1.9	−1.4	−2.3	−0.2	−1.0	−0.8	−3.8
Mean: −1.76 St. dev.: 1.02 St. error: 0.36									
CHANGE WITH 2 CC. MERCUPURIN FROM VALUES FOUND AT THE END OF THE AMMONIUM CHLORIDE RÉGIME									
Change in plasma vol. with 2 cc. mercupurin from values after NH_4Cl administration	−555	−220	−490	−170	−100	−380	−460	−110	−480
Mean: −329.4 St. dev.: 169 St. error: 59.7									
% change in hematocrit	+28.2	+11.0	+13.8	+14.3	+2.6	+26.6	+19.5	+9.2	+8.5
Mean: +14.85 St. dev.: 8.01 St. error: 2.83									
% change in serum protein concentration	+10.2	+9.0	+17.2	+10.0	+23.4	+32.0	+13.8	+13.8	
Mean: +15.2 St. dev.: 7.42 St. error: 2.80									
Change in body weight (kg.)	2.0	2.8	14	3.5	0.7	2.4	3.1	1.8	1.6
Mean: −2.14 St. dev.: 0.83 St. error: 0.29									
CHANGE RESULTING FROM BOTH AMMONIUM CHLORIDE AND MERCUPURIN COMPARED TO THE CONTROL DETERMINATION									
Total change in plasma vol. with NH_4Cl and 2 cc. mercupurin from control determinations	−955	−430	−550	−600	−1160	−1050	−470	−250	−1110
Mean: −730 St. dev.: 270 St. error: 95.4									
% change in hematocrit	+18.8	+3.9	+4.8	+8.5	+3.7	+24.0	+6.7	+4.2	+9.4
Mean: +9.33 St. dev.: 6.74 St. error: 2.42									
% change in serum protein concentration	+12.2	−24.3	+27.1	−2.7	+47.5	+32 3	+7.2	+9.4	
Mean: +17.47 St. dev.: 15.14 St. error: 5.71									
Total change in body weight (kg.)	−3.6	4.9	3.3	4.3	3.0	2.6	4.1	2.6	4.8
Mean: −3.68 St. dev.: 0.33 St. error: 0.12									

caloric consumption. Nine grams per day of ammonium chloride in enteric coated tablets were ingested. At the conclusion of this régime which varied from 3 to 19 days, the measurements were repeated, and a 2 cc. intravenous injection of mercupurin was then given. The observations were again made 24 hours later to evaluate the effect of the mercupurin injection.

The subject was weighed in the rested postabsorptive state on a beam balance accurate to 2 gm. After the weighing he was placed on a table and blood was withdrawn for the determination of the plasma volume,[7] hematocrit,[18] and total serum protein concentration.[1] The total circulating protein may be calculated from the product of the plasma volume and the serum protein concentration.

Results. The alterations in plasma volume and body weight as well as the percentage change in plasma volume, hematocrit, serum protein concentration, total circulating protein and body weight are recorded in Table 1. The second portion of this table deals with changes resulting from the injection of mercupurin on the partially dehydrated subject.

With the administration of 2 cc. of mercupurin alone to 10 normal subjects on the normal diet, a weight loss of 1.73 ±0.3 kg. (2.6±0.5%) was produced in 24 hours, and it was associated with a loss in plasma volume of 544±88 cc. or 15.7 ±2.4%.[13] A low salt diet and ammonium chloride in the subjects reported here produced a greater weight loss of 3.1±0.58% than that experienced by the subjects who received mercupurin alone. The decrease in plasma volume, however, was not as great in spite of the weight loss and amounted to 403±11.4 cc. or 13.8±3.8%. The administration of mercupurin to these already dehydrated subjects produced a further loss of weight of 3.94±0.52% which was considerably larger than that experienced by the normal subjects receiving mercupurin alone. The change in plasma volume was smaller in these dehydrated subjects and amounted to only 329±59.7 cc. The relative change of plasma volume, 13.1±2.5%, was not significantly different from the change in plasma volume with mercupurin alone.

The effect of the combined administration of the low salt diet, ammonium chloride, and mercupurin produced a decrease in the body weight from the control determinations of 3.68±0.12 kg. or 6.7± 0.4%. This was accompanied by a mean decrease in plasma volume of 730±95 cc. or 25.2±3.96%.

For the purpose of comparison the mean change in plasma volume and body weight induced by: (1) a 2 cc. injection of mercupurin without previous preparation with ammonium chloride; (2) ammonium chloride and a low salt diet; (3) by 2 cc. intravenous injection of mercupurin following ammonium chloride administration; and (4) the total effect of the low salt diet, ammonium chloride, and 2 cc. of mercupurin are shown in Figure 1. It will be noted that the mean change in plasma volume following the injection of mercupurin in the subjects on a low salt diet and ammonium chloride (Column 3) was significantly smaller than that found in subjects on their usual diet who received a similar injection of mercupurin (Column 1). These changes may be more directly compared when expressed as mean percentage change from previous determination as illustrated in Figure 2. The third column represents mean percentage change produced by mercupurin from the values of plasma volume and body weight noted after the administration of ammonium chloride. The fourth column is the mean percentage change from the control determinations.

The mean percentage change in the serum protein concentration and total circulating protein are of considerable interest and are shown graphically in Figure 3. The serum protein concentration may increase to some extent with the loss of plasma volume resulting from dehydration, but the change is proportionately less than the change in plasma volume. Thus there is a loss of total circulating protein. This decrease in total circulating protein was noted when the plasma volume

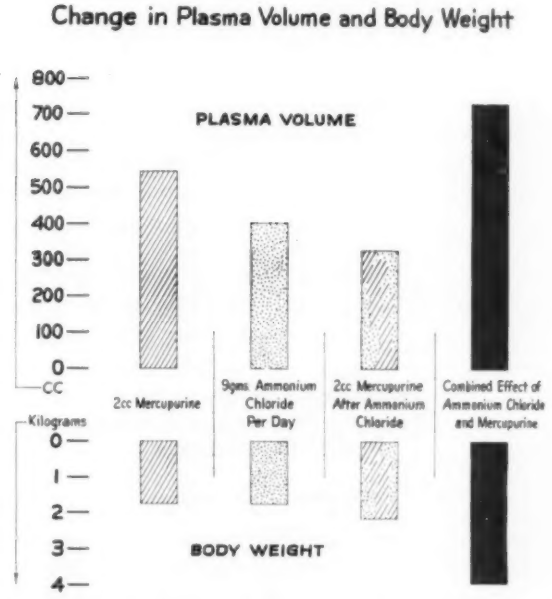

FIG. 1.—A comparison between the decrease in plasma volume and body weight in normal subjects after (1) 2 cc. of mercupurin; (2) a low salt diet and ammonium chloride; (3) after 2 cc. mercupurin from the values produced by the low salt diet and ammonium chloride; (4) the combined effect of the low salt diet, ammonium chloride followed by 2 cc. of mercupurin.

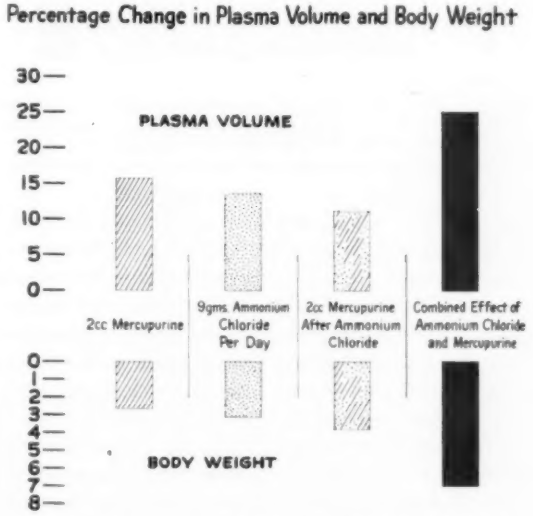

FIG. 2.—A comparison of the relative change in plasma volume and body weight in normal subjects after (1) 2 cc. of mercupurin; (2) a low salt diet and ammonium chloride; (3) 2 cc. mercupurin from the values produced by the low salt diet and ammonium chloride, and (4) the combined effect of the low salt diet, ammonium chloride, followed by 2 cc. mercupurin.

was decreased by mercupurin alone or by ammonium chloride. When mercupurin was administered after preparation with ammonium chloride, however, the total circulating protein did not change and the serum protein concentration increased considerably. It will also be noted in Figure 2 that under these circumstances in spite of a greater loss of water, there was less change in the plasma volume than might have been expected if as extensive a diuresis had resulted from mercupurin or ammonium chloride alone.

ing the ammonium chloride administration in spite of a good diuresis; both, however, experienced not only a good diuresis with mercupurin, but also greater loss in plasma volume than many of the other subjects.

Discussion. It is apparent from these results that the combination of a low salt diet and ammonium chloride followed by a 2 cc. intravenous injection of mercupurin will produce a considerable degree of dehydration in the normal individual which in these cases amounted to a mean loss

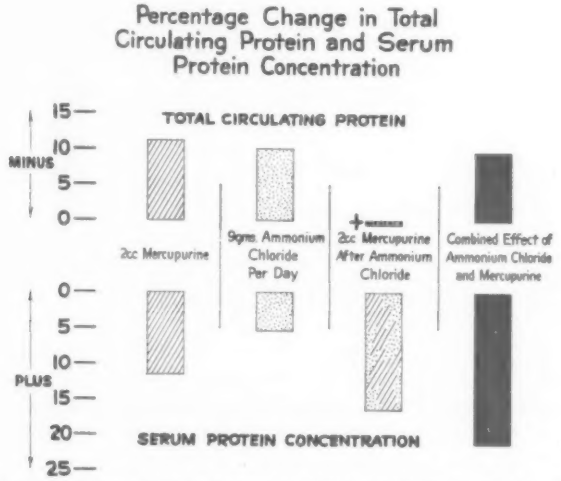

FIG. 3.—A comparison of the relative changes in total circulating protein and serum protein concentration after (1) 2 cc. mercupurin; (2) a low salt diet and ammonium chloride; (3) after 2 cc. of mercupurin from the values produced by the low salt diet and ammonium chloride, and (4) the combined effect of the low salt diet and ammonium chloride followed by 2 cc. of mercupurin.

With the administration of a low salt diet and ammonium chloride, the hematocrit in 8 of the cases completely failed to indicate the direction of change of the plasma volume or the extent of the change, and frequently fell as the plasma volume was decreased. Following the injection of mercupurin, however, the hematocrit closely reflected the further dehydration of the plasma volume, and in many instances the percentage change in plasma volume. Another point of some interest was the extent of the change in the plasma volume induced by mercupurin. Two cases (Nos. 3 and 7) did not have a significant change in the plasma volume following the ammonium chloride administration in spite of a good diuresis; both, however, experienced not only a good diuresis with mercupurin, but also greater loss in plasma volume than many of the other subjects.

of weight of 3.68 ± 0.12 kg., or $6.72 \pm 0.42\%$ of the body weight. A diuresis of this degree is not uncommonly experienced in patients with heart failure and edema. Should such a diuresis occur in a formerly edematous patient, it should not necessarily be looked upon as evidence of "subclinical" edema.

It may also be noted that the diuretic effect of the low salt diet and ammonium chloride in the normal subjects was somewhat greater than that experienced with mercupurin alone. This is contrary to the usual clinical impression formed while dealing with edematous patients in whom mercupurin usually produces a greater

diuresis. This may be explained by the fact that with the administration of ammonium chloride to the normal subject there is a loss of both intracellular and extracellular fluid.[3,5,10,17] The weight loss following mercurial diuretics is, on the other hand, almost entirely at the expense of the extracellular fluid.[2] It would seem likely then that in normal subjects ammonium chloride affecting both the extracellular and intracellular fluid compartments might produce a somewhat greater diuresis, while with edematous subjects where there is an excessive accumulation of extracellular fluid, a greater diuresis might be experienced with mercupurin.

In spite of a slightly greater weight loss, the change in plasma volume after ammonium chloride was somewhat less than that experienced after mercupurin alone. This might be expected if mercupurin has a greater effect on the extracellular fluid.

The weight loss in this group of 9 subjects with the low salt diet and ammonium chloride was not as great as that reported in a previous study of normal subjects who received the diet and ammonium chloride for a period of 3 to 4 days.[11] This may in part be due to the selection of cases since some of these cases had experienced relatively little diuresis early in the régime and therefore it was continued for a longer period before the plasma volume and body weight were again measured. It is apparent, however, that continuing the régime over several days does not significantly increase the loss of weight.[11]

Of considerable interest was the diuresis experienced following mercupurin injection in these subjects who had already lost approximately 3% of the body weight on the low salt ammonium chloride regimen. The rôle of the acid salts in enhancing the diuretic effect of the mercurial diuretics is well known[4,8,9,15] and it appeared to exert a similar rôle, as expected, in these normal subjects. The weight loss with mercupurin alone was $2.64 \pm 0.5\%$ of the body weight. On the other hand, the weight loss induced by mercupurin after preparation with a low salt diet and ammonium chloride was $3.94 \pm 0.5\%$ of the body weight in spite of the associated dehydration with such a preparation. However, with the greater diuresis there was less change in the plasma volume than was noted after the administration of either ammonium chloride or mercupurin alone, Figure 2. With mercupurin alone, the loss of plasma volume accounted for $26.3 \pm 3.8\%$ of the loss of body weight; after ammonium chloride preparation the loss of plasma volume following injection of mercupurin accounted for only $16.5 \pm 4.2\%$ of the loss of body weight.

With the diuresis following the administration of ammonium chloride or the injection of mercupurin without previous preparation, the decrease in plasma volume was accompanied by a decrease in the total circulating protein and by a relatively small increase in the serum protein concentration as noted in Figure 3. On the other hand, the more extensive diuresis produced by mercupurin in the already dehydrated subject after ammonium chloride administration was not accompanied by a similar decrease in the total circulating protein and the fall in plasma volume of 13.1% was associated with an increase in the serum protein concentration of 15.2%. It would appear likely that this increase in the serum protein concentration prevented a greater decrease in the plasma volume under these circumstances even though there was a more extensive diuresis. The possibility is suggested by these findings that the total circulating protein may be quite labile with small losses of body fluid, but when greater degrees of dehydration occur the protein is held in the blood stream. There is probably a limit to the loss of plasma volume with dehydration due to the fact that the serum protein held in the blood stream in higher concentrations will support the plasma volume in spite of dehydration of the tissues.

The changes in the hematocrit appeared to be similar in many ways to the changes in the serum protein concentration. With the milder forms of dehydration the hem-

atocrit failed completely to indicate the changes in the plasma volume. This has been noted before.[11,12,13,14] With further dehydration induced by mercupurin after the low salt diet and ammonium chloride there was a considerably greater change in the hematocrit which more closely reflected the further depletion in the plasma volume. It is possible that the measurement of plasma volume by the dye dilution method may reflect changes in the capillary circulation with mild dehydration before the relationship of cells to plasma in the large vessels is disturbed. When more extensive dehydration occurs, then the relationship of cells to plasma in large vessels will parallel the change in plasma volume.

All of these subjects exhibited some symptoms suggestive of an inadequate circulation on the day following the injection of mercupurin. They complained of weakness, prostration, fatigue, and some felt so faint in attempting to stand that they chose to remain in bed. There was a decrease in the pulse pressure and venous pressure and an increase in the basal pulse rate, though these were not regularly recorded in this group, which would also suggest a decrease in the volume of their circulation. In some instances, the dehydration was so complete that it suggested the clinical and circulatory defect frequently noted in early shock.

Conclusion. The administration of a low salt diet, ammonium chloride, and mercupurin to 9 normal subjects resulted in a mean loss of 3.68 ± 0.12 kg. or $6.72 \pm 0.42\%$ of the body weight. This diuresis was associated with a mean fall in plasma volume of 730 ± 95 cc. or $25.17 \pm 3.9\%$. The diuretic effect in normal subjects of a 2 cc. injection of mercupurin, of a low salt diet and ammonium chloride and of a 2 cc. injection of mercupurin after preparation with a low salt diet and ammonium chloride are compared.

Though diuresis resulting from a 2 cc. injection of mercupurin is increased by the preparation with a low salt diet and ammonium chloride, the change in plasma volume under these circumstances is less pronounced. This may be associated with the fact that the preparation with a low salt diet and ammonium chloride produces an initial fall in plasma volume and total circulating protein. Subsequent loss of fluid is not followed by further decrease in total circulating protein so that the increased concentration of serum protein may tend to prevent larger changes in the plasma volume.

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THE RELATION OF ARTERIAL PULSE-PRESSURE TO ARTERIOVENOUS OXYGEN DIFFERENCE, ESPECIALLY IN ARTERIAL HYPERTENSION

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Pulse-pressure in the brachial artery is no longer regarded as even a rough measure of cardiac output. Nor can we assume that it gives information concerning what is happening in other arteries. Furthermore, arterial distensibility decreases and pulse-pressure increases as internal pressure is raised, although deviations due to this factor are small in the range of human blood pressures.[9] Comparisons involving pulse-pressure from different individuals (varying in size of vessels, muscle masses, metabolic rates, etc.) taken under varying conditions of temperature, humidity, and so forth, would seem therefore, to have little justification.

In spite of these considerations, an attempt was made to correlate certain data obtained from a number of patients of both sexes suffering from a variety of diseases. In Figure 1 the arteriovenous oxygen differences have been plotted against the products of the pulse pressure multiplied by pulse rate (PP $\times$ PR) as ascertained on the brachial artery. Venous blood was drawn from the median basilic vein, and arterial blood usually from the brachial or sometimes from the femoral artery. It will be seen that most of these cases fall within a curved area (AA), the mean of which is roughly represented by a curve (DD) such that, for any point on the curve, (PP $\times$ PR) $\times$ (A–V O_2 diff.) = K_1, a constant. (The shaded area E represents the "normal" area.) (1)

The oxygen consumption of an arm at rest can be assumed to be constant and equal to the product of the volume of blood entering or leaving the arm per minute (V) and the volume of oxygen lost by each 100 cc. of blood while traversing the arm, or,

$$V \times (A\text{–}V\ O_2\ \text{diff.}) = K_2 \qquad (2)$$

If equation (1) above correctly expresses a general relationship between these two variables, it follows that V varies directly as, or is proportional to, PP $\times$ PR. The latter can therefore be used as a fair clinical indication of blood flow through the arm.

On further inspection it was found: (*a*) that those cases falling in the lower portion of the "curved area," with circulatory stasis, are all, as might be expected, cases of cardiac disease (valvular disease, calcified pericarditis, emphysema), cancer, certain severe anemias, and so forth, (*b*) that those cases falling in the upper part of the "curved area," with a large pulse pressure and a rapid passage of blood through the tissues, are nearly all cases of arterial hypertension and certain other cases of anemia with low diastolic pressures, and (*c*) that those cases known to have a lowered basal metabolic rate fall to the left, and those with an increased BMR fall to the right of the "curved area." These cases are omitted from Figure 1.

Arterial Hypertension. Since the above results were published in 1941,[4] we have attempted to use the graph in Figure 1, to throw light on certain aspects of the phenomena of arterial hypertension. We therefore examined an additional group of hypertensive patients, selecting those without symptoms of cardiac failure, who were, as a rule, attending hospital for some other disease, and in whom the hypertension was discovered only on routine examination. In all cases the diastolic pressure was 90 or more. Again, the results show

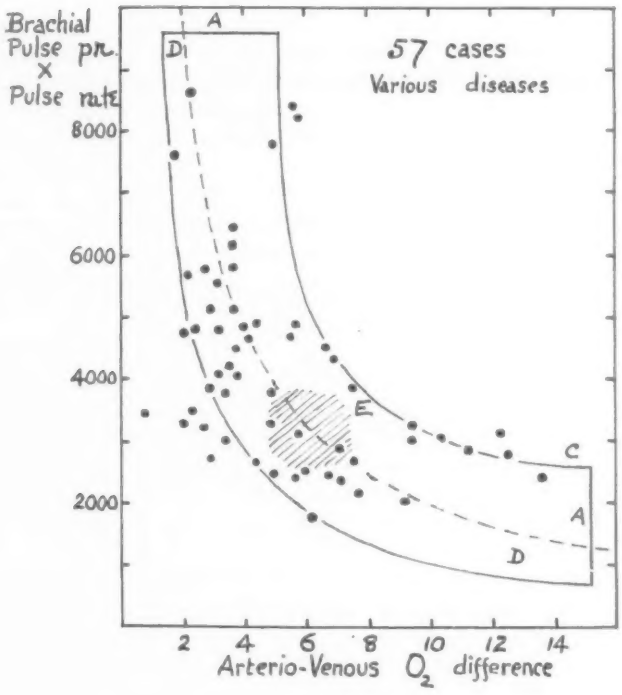
Brachial
Pulse pr.
X
Pulse rate
8000
6000
4000
2000
A
D
57 cases
Various diseases
E
C
A
D
2
4
6
8
10
12
14
Arterio-Venous O_2 difference

FIG. 1.

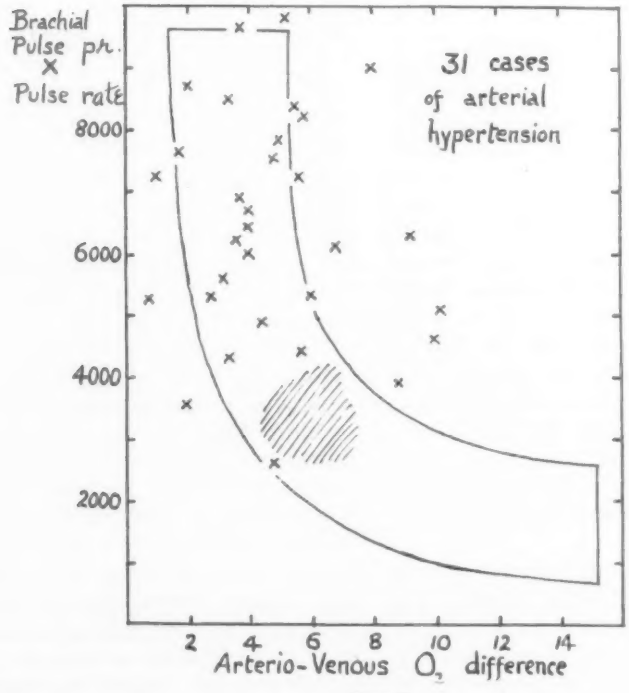
Brachial
Pulse pr.
X
Pulse rate
8000
6000
4000
2000
31 cases
of arterial
hypertension
2
4
6
8
10
12
14
Arterio-Venous O_2 difference

FIG. 2.

that, in general, these cases fall at the upper end, and in some cases to the right of, the "curved area" (Fig. 2).

Since these experiments seemed to offer the additional opportunity to investigate certain aspects of the old controversial question of the relation of blood chlorides to arterial hypertension, we also determined the arteriovenous whole blood chloride differences (Eisenman's method)[7] for comparison with the arteriovenous oxygen differences (Fig. 3).

Since the cardiac output per minute in hypertensives is not increased (or if anything, even diminished),[6] and the blood flow through the limb is increased it follows that the volume of blood flowing through the viscera must be diminished, *i. e.*, that general vasoconstriction is more marked in viscera than in limbs, and may even be absent in the limbs.

From these results it would seem that, instead of regarding variations in pulse-pressure as indications of similar variations

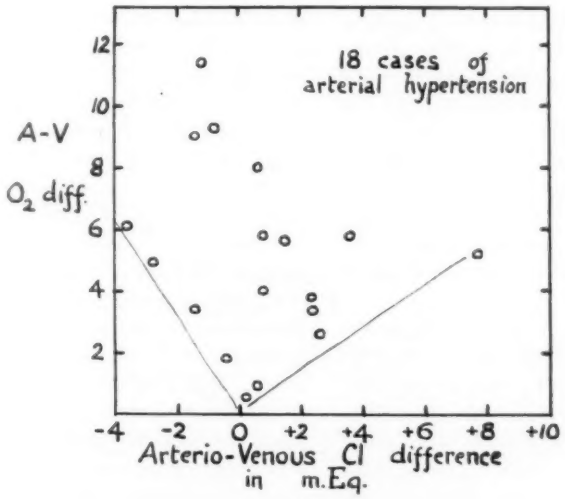

FIG. 3.

Discussion. (A) *Blood Flow in Limbs and Viscera.* It has often been assumed that, in arterial hypertension, the vasoconstriction more or less equally involves all of the peripheral arterioles, whether in limbs or in viscera. This conception was supported by the work of Prinzmetal and Wilson[12] and of Pickering[11] (using plethysmographic methods) which indicated that the blood flow through the arms was unchanged in hypertension. On the other hand Grant and Pearson,[8] Abramson,[1] and Apperly and Cary[4] (the last named using the method here described) showed an increased blood flow through the arms in hypertension. Grant[8] and Abramson[1] further demonstrated that the same holds true for the calf of the leg.

in cardiac output, we should rather regard them as indicating the varying use of the limbs as a "blood shunt," *i. e.*, that the high pulse-pressure of hypertension and some anemias indicates that a larger (and the low pulse-pressure of circulatory failure a lower) proportion of the total blood volume is being shunted through the limbs, and possibly through all muscle masses. The value of such an arrangement for reciprocally varying muscular and visceral needs is of course obvious. It is of interest that epinephrine produces the same results.

It was remarked above that in the cases of those people known to have a high BMR, their points fell to the right of the "curved area," which indeed was to be

expected. As is well known, the BMR is also increased in cases where the heart has increased work to do, as in arterial hypertension, chronic valvular disease and many cases of severe anemia. At first sight therefore we might expect that many of our cases of hypertension would also fall to the right of the curve, or in other words, that the upper end of the "curved area" in Figure 2 would always be bent to the right. On further consideration, however, this displacement is not so clear. For if the higher BMR is due entirely to the increased cardiac work we would expect conditions in the arm to be unaffected and therefore the points on the graph to be scattered along the median curve DD. The fact, however, that many of the points representing these cases are displaced to the right of the curved area indicates, unexpectedly, that the oxygen consumption in the arm is also augmented and that probably the increased metabolism is general.

(B) *The Chlorides in Arterial Hypertension.* Until recent years there was much discussion and conflicting opinion concerning the work of Allen and Sherril,[2,3] who demonstrated the common association of hyperchloremia (in venous blood) with arterial hypertension, and claimed good therapeutic results from salt deprivation. We also showed that, on the whole, the blood chloride was raised, but found that the chloride spread among the hypertensives considerably overlapped that of our normal subjects.[5] Schmitt and Basse[13] obtained the same results in chronic nephritis but, on the whole, contrary results in essential hypertension.

The results quoted above were obtained from venous blood. Now it is known that generally, with increasing blood stasis, as in cardiac failure even without edema, there is a loss of chloride from the blood into the tissues, and the venous blood chloride falls.[10] Conversely, it might be expected that when the blood flow through the tissues increases above normal the venous blood chloride would be higher than normal. The increased blood flow through the arm in essential hypertension might therefore possibly account for the generally increased blood chloride, as determined in venous blood from the arm. In that case the arteriovenous oxygen differences should have (*a*) a direct relationship with arteriovenous chloride differences and (*b*) an inverse relationship with venous blood chlorides.

Figure 3 shows that these simple relationships were not realized. It is true that when the A–V oxygen difference was very small, *i. e.*, a large blood flow through the arm, the A–V chloride difference was also small. The blood, in fact, was rushed through the tissues too rapidly to allow time for A–V differences to occur. As the A–V oxygen difference increased, however, the A–V chloride differences also increased, but in varying directions, some positively and some negatively.

These results obviously show that two or more factors, acting in opposite directions, are at work. Attempts to correlate these changes with pulse-pressure, diastolic pressure, or the ratio of the former to the latter, were fruitless. The final direction of the chloride shift during the passage of blood through the arms as the A–V oxygen difference increases (*i. e.* with increasing stasis), is probably the resultant of at least two forces: (*a*) with increasing stasis there is a rising capillary pressure and increased transudation of water and salts, including chlorides. Since the concentration of chlorides in plasma is greater than that in red cells, this means a loss of chlorides from the blood as a whole and hence a positively increasing A–V chloride difference. (*b*) With increasing stasis there is also increasing accumulation of carbon dioxide in the tissues, with consequent shift of chloride from tissues to capillary blood, and hence an increasingly negative A–V chloride difference. Whether the condition of the lungs or other organs determine which of these two factors will predominate is unknown. It would appear, however, from these and from our earlier studies,[5] that there is no constant relationship between blood chlorides and arterial

hypertension, and that the factors governing the former are complex.

Conclusions. 1. Since pulse-pressure × pulse rate × arteriovenous oxygen difference in the arm of different subjects roughly equals a constant, PP × PR is regarded as a fair index of blood flow entering the arm.

2. Since PP × PR is increased and A-V O_2 difference is diminished in the limbs in arterial hypertension (in which total cardiac output is not increased), it follows that a larger proportion than normal of total blood flows through the limbs (and possibly all muscle masses), *i. e.*, peripheral vasoconstriction is absent or less marked in the limbs than in the splanchnic area. Hence the increasing pulse-pressure commonly found with increasing hypertension.

3. In patients with high metabolic rates, the points on the graph are moved to the right of the normal curve, indicating an increased oxygen consumption in the arm. The fact that many cases involving increased cardiac work also move to the right shows that the increased metabolism in these cases is not due to increased cardiac work alone, but takes place in the arms also and is possibly a general condition.

4. It is suggested that the pulse-pressure serves as a rough but valuable indication of the reciprocally varying needs and blood supply of the viscera and muscular masses of the body.

5. No relation could be found between hypertension and blood chlorides.

We are indebted to Dr. W. B. Porter, Professor of Medicine, and to Drs. G. Watson James and Oscar Clarke, Assistant Residents in Medicine, for valuable help and advice.

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THE AGGLUTINATION REACTION FOR HEMOLYTIC STREPTOCOCCI IN RHEUMATOID ARTHRITIS; ITS SIGNIFICANCE IN DIAGNOSIS AND TREATMENT*

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It is rather remarkable that rheumatoid arthritis, which is obviously a systemic disease and one which can induce such marked changes in joint tissue, should be characterized by so few demonstrable changes in the physiology and chemistry of the body. This statement applies particularly to the various components of the blood and urine and even of the joint fluid. To be sure, the sedimentation rate is elevated in a very high percentage of cases, but so it is in many other systemic diseases; and a similar elevation is noted in all other inflammatory conditions of the joints. The frequently noted anemia and leukocytosis are equally non-specific and provide very little aid to an accurate diagnosis. The only really specific reaction so far described for rheumatoid arthritis is the streptococcal agglutination reaction. Agglutinins for the *Streptococcus hemolyticus* were first demonstrated in the serums of patients with rheumatoid arthritis in 1930 by Cecil, Nicholls and Stainsby,[3] who showed that most of the attenuated hemolytic strains recovered from arthritic patients were agglutinable with rheumatoid serum, often in rather high dilutions. In a series of 103 cases of rheumatoid arthritis, 97 showed agglutination with the "typical strain" of streptococcus at a dilution of 1 to 640 or higher, while in a series of 50 normal controls the serum in every case failed to give a strong agglutination reaction. Nicholls and Stainsby[20] noted that hemolytic streptococci from other sources, such as scarlet fever and erysipelas, were often agglutinable with arthritic serum. These results were confirmed by Dawson, Olmstead and Boots[7] and many others. It has also been found that the serums of patients with rheumatoid arthritis frequently give a positive precipitation reaction with the protein fractions of *S. hemolyticus*.

Table 1 summarizes the results obtained by various investigators with respect to the incidence of specific agglutinins for the *S. hemolyticus* in the serums of rheumatoid patients.

The object of this investigation was to determine the present status of the streptococcal agglutination reaction in rheumatoid arthritis and to find out, if possible, the effect of gold therapy on this interesting phenomenon.

In this study we have investigated: (1) the optimal conditions under which the agglutination reaction against the hemolytic streptococcus should be carried out; (2) the incidence of streptococcal agglutinins in sera (*a*) of patients with typical rheumatoid arthritis of varying duration; (*b*) of patients with other joint diseases; (*c*) of patients suffering from streptococcal infections; (*d*) of normal controls; and (3) the incidence of streptococcal agglutinins in patients with rheumatoid arthritis before and after treatment with gold salts.

Material and Methods. Antistreptococcal rabbit sera were used for positive controls and in tests designed to study the optimal conditions of the reaction. The sera were prepared by repeated intravenous injections of rabbits with formalin-killed Group A hemolytic streptococci (strain AB13 or strain

* Aided by a grant from the John and Mary R. Markle Foundation, the Ophthalmological Foundation, and the Dazian Foundation for Medical Research, New York.

NY5). Only sera having an agglutinin titer for the homologous strain of at least 1 to 640 were employed.

For the study of human sera approximately 5 cc. of blood were withdrawn from a cubital vein and transferred into a sterile test tube. After retraction of the clot and short centrifugation, the clear supernatant serum was removed with a sterile capillary pipette and stored without preservative in the ice box until used. The sera were usually examined within 1 to 2 weeks after withdrawal.

addition of 0.2% formalin. Killed suspensions kept in the ice box at approximately + 4° C. can be used for 1 week.

Reaction. Five-tenths cc. quantities of serial dilutions of the sera in 0.9% saline solution from 1 to 10 to 1 to 2560 were mixed with 0.5 cc. quantities of the antigen, thus making final dilutions of the sera from 1 to 20 to 1 to 5120. All reactions were carried out in 10 × 75 mm. Pyrex test tubes.

Controls. The following controls were made: (1) antigen + saline; (2) serial dilutions of a normal serum of the same species

TABLE 1.—REVIEW OF LITERATURE (1930–1942) CONCERNING PRESENCE OF STREPTOCOCCAL AGGLUTININS IN THE BLOOD OF PATIENTS SUFFERING FROM RHEUMATOID ARTHRITIS

Author	No. of patients studied	% of positive reactions
Cecil, Nicholls and Stainsby[3]	103	94.0
Nicholls and Stainsby[20]	110	93.6
Gray and Gowen[14]	60	75.0
Dawson, Olmstead and Boots[7]	206	55.0
Gray, Fendrick and Gowen[15]	144	69–80
Ashworth[1]	65	89.2
Clawson, Wetherby, Hilbert and Hilleboe[5]	60	59.5
Keefer, Myers and Oppel[18]	22	54.5
Nicholls and Stainsby[21]	613	45.0
Cox and Hill[6]	41	71–81
Dawson, Olmstead and Jost[8]	71	56.3
Wainwright[23]	51	54.9
Blair and Hallman[2]	62	82.0
Gray, Bernhard and Gowen[16]	200	70–76
McEwen, Bunim and Alexander[19]	36	56.0
Goldie and Griffiths[13]	28	89.0
Hartung, Davis, Steinbrocker and Straub[17]	50	36.0
Short, Dienes and Bauer[22]	47	53.1
Ferry and Hunt[12]	36	58.0

Antigen. Living and killed cultures of two strains of Group A hemolytic streptococci (AB13 and NY5) were used. The stock cultures of these strains were kept in 5% blood broth in the ice box and transferred every month.

Experiments With Living Cultures. Eighteen hour broth cultures were used; these were prepared by transferring 0.5 cc. quantities of stock culture into bottles containing 100 cc. of veal infusion broth.

Experiments With Killed Cultures. Eighteen hour broth cultures, prepared in the same manner as those for the experiments with living organisms, were centrifugalized for 30 minutes at 2000 r.p.m. and the sediment resuspended in an amount of 0.9% saline solution equal to one-half the volume of the original culture. The saline suspension of the organisms was then killed by heating for 1 hour in a water bath at 60° C. In some instances the cultures were killed by the

(human or rabbit) + antigen; (3) serial dilutions of a positive serum of the same species (human or rabbit) + antigen; (4) each serum to be tested + saline and (5) each control serum + saline. Only experiments in which Controls 1, 2, 4 and 5 were negative and Control 3 positive were considered acceptable.

Incubation Method. The serum-antigen mixtures were incubated for 2 hours at 56° C. and then kept overnight in the ice box at 4° C. Readings were made after refrigeration.

Centrifugation Method. The serum-antigen mixtures were immediately centrifugalized for 15 minutes at 2000 r.p.m. and readings made immediately thereafter. The reactions were read by daylight. Those in which flocculation was grossly visible after gentle tapping of the tubes were recorded as positive. The procedure was similar to that

previously described by one of the authors (deGara) in experiments with pneumococci.[11]

Results. *Study of Optimal Conditions for the Detection of Streptococcal Agglutinins.* The agglutinin titers obtained with the incubation and centrifugation methods with living and killed antigens were compared, making use of an antistreptococcal rabbit serum, the serum from a patient with rheumatoid arthritis, and normal rabbit and human sera (Table 2).

reactions were found with sera from normal men or normal rabbits.

In order to determine what concentration of antigen would give optimal reactions with the serum agglutinins over a wide range of dilutions, killed suspensions were prepared from cultures containing from 50 million to 300 million organisms per cc. The various suspensions were then tested with a known potent antistreptococcal rabbit serum (Table 3).

TABLE 2.—COMPARISON OF INCUBATION AND CENTRIFUGATION METHODS FOR DECTECTION OF AGGLUTININS WITH HEMOLYTIC STREPTOCOCCI (STRAIN AB13) IN SERA OF RABBITS AND MEN

Serum	Antigen	Method	Agglutination titer
Immune rabbit	Living culture	Incubation	1:320
	Killed culture	Incubation	1:320
	Killed culture	Centrifugation	1:2560
Normal rabbit	Living culture	Incubation	Neg.
	Killed culture	Incubation	Neg.
	Killed culture	Centrifugation	Neg.
Patient with rheumatoid arthritis	Living culture	Incubation	1:160
	Killed culture	Incubation	1:160
	Killed culture	Centrifugation	1:640
Normal human	Living culture	Incubation	Neg.
	Killed culture	Incubation	Neg.
	Killed culture	Centrifugation	Neg.

TABLE 3.—RELATION OF DENSITY OF STREPTOCOCCAL SUSPENSION TO DETECTION OF AGGLUTININS IN ANTISTREPTOCOCCAL RABBIT SERUM

Antigen: AB13 saline suspension (killed at 60° C. for 60 minutes).

Density (organisms per cc.)	Agglutination* by dilution of antistreptococcal rabbit serum of:								
	1:20	1:40	1:80	1:160	1:320	1:640	1:1280	1:2560	1:5120
300,000,000	+++	+++	+++	+++	+++	++	+	+	–
200,000,000	+++	+++	+++	+++	++	++	+	+	–
150,000,000	+++	+++	+++	+++	++	++	+	+	–
100,000,000	++	+++	+++	+++	++	++	+	–	–
75,000,000	++	++	++	++	+	+	–	–	–
50,000,000	–	+	++	++	+	–	–	–	–

* – means negative. + means small clumps, supernate turbid. ++ means small clumps, supernate clear. +++ means large clumps or firm disk, supernate clear.

The titers obtained by the incubation method were the same, whether living or killed cultures were used as antigens. The titers yielded by the centrifugation method were definitely higher than those by the incubation method (Table 2). Since the same killed culture was employed with both methods, the results are comparable and indicate that the centrifugation provides a more sensitive method for the detection of streptococcal agglutinins than does the incubation method. No positive

With a weak bacterial suspension containing approximately 50 million organisms per cc., reactions were obtained only in serum dilutions up to 1 to 320, and there was a definite inhibition of the reaction in the zone of antibody excess. The range of the reaction with denser suspensions, containing 75 million or 100 million streptococci per cc., increased in width, but the full range was obtained only with an antigen prepared from a culture containing at least 150 million

organisms per cc. (Table 3). Since 18 hour broth cultures of the strains used contained approximately 75 to 100 million organisms per cc., the sediment of these cultures was resuspended in an amount of saline equal to one-half the amount of the original broth culture; then the saline suspension was immediately killed by heat, as described above. These suspensions contained approximately 150 to 200 million organisms per cc. and were used for the reactions with sera from men or from animals.

of streptococcal agglutinins in the sera obtained from 480 persons. The criteria for identification of rheumatoid arthritis were the following:

Rheumatoid Arthritis. (1) Presence of fusiform fingers, (2) multiple joint involvement, (3) presence of subcutaneous nodules, (4) typical Roentgen ray appearance of the bones and joints, and (5) acceleration of the sedimentation rate of the red blood cells. Only cases that presented at least 3 of these 5 symptoms were included in our series. Patients who had had rheumatoid arthritis for less than 1 year were classified as early, those with a rheumatoid history of more than 1 year, as late cases.

TABLE 4.—INCIDENCE OF STREPTOCOCCAL AGGLUTININS IN HUMAN SERA UNDER NORMAL AND PATHOLOGIC CONDITIONS

Clinical diagnosis	No. of cases	Cases having agglutinins in a serum dilution of 1:160 or higher	
		No.	%
Rheumatoid arthritis:			
"Late"	190	126	66.3
"Early"	78	36	46.1
Total	268	162	60.4
Subacute infectious arthritis	6	3	50.0
Ankylosing spondylitis (Marie-Strümpell)	16	1	6.2
Osteoarthritis	95	1	1.0
Gonococcal arthritis	4	0	0.0
Various other joint diseases	48	0	0.0
Rheumatic fever	8	0	0.0
Scarlet fever	8	2	25.0
Normal controls	27	0	0.0
Total	480		

The agglutinin titer for 2 different strains of hemolytic streptococci (AB13 and NY5) was studied in 110 sera from patients with rheumatoid arthritis. It was found that 73 of them (66%) had approximately the same titer for both strains, while differences were noted in the remaining 37 sera (34%). Of these, 19 showed a higher titer for strain AB13, and 18 contained more agglutinins for strain NY5.

The centrifugation and incubation methods were simultaneously carried out on 110 sera from patients with rheumatoid arthritis. Of these 66 (60%) gave approximately the same results with both methods, while in the remaining 44 instances (40%) higher titers were observed with the centrifugation method.

Incidence of Streptococcal Agglutinins in Human Sera. Table 4 shows the incidence

Subacute Infectious Arthritis. In this group cases of arthritis following acute infectious diseases were included.

Various Other Joint Diseases. This group comprises patients suffering from intermittent hydroarthrosis, menopausal arthrosis, gouty arthritis, and various joint conditions not included in the other groups.

The criteria used for the diagnoses of gonococcal arthritis, ankylosing spondylitis (Marie-Strümpell), osteoarthritis, and scarlet fever were those generally employed. A few cases of rheumatic fever with rheumatic carditis were also included.

Normal Controls. Sera from healthy individuals of various ages and sexes that

had no subjective or objective symptoms of arthritis were used.

Table 4 shows that 60.4% of the patients with rheumatoid arthritis had agglutinins for hemolytic streptococci in a serum dilution of at least 1 to 160. There was, however, a considerable difference between the sera from late cases, 66.3% of which contained agglutinins, and those from early cases, where they were found in only 46.1%. Of the 6 sera from patients with subacute infectious arthritis, 3 (50%) contained antistreptococcal agglutinins; 2 of 8 sera from persons with scarlet fever (25%) agglutinated hemolytic streptococci in a titer of 1 to 160 or higher. One of 16 patients with ankylosing spondylitis (Marie-Strümpell) who also suffered from rheumatoid arthritis had agglutinins for hemolytic streptococci in his serum. Of 95 patients with osteoarthritis, only 1 had agglutinins for streptococci. No agglutinins were found in the remaining 60 sera from patients suffering with gonococcal arthritis, various other joint diseases, or with rheumatic fever, and none were present in those of the 27 normal controls.

Degree of severity*	Total No. examined	Cases with agglutinins	
		No.	%
Mild	82	38	46.3
Moderately severe	145	97	66.8
Severe	41	27	65.8
Total	268	162	60.4

* Mild cases, ambulant. These patients were still able to work every day, and had only a moderate degree of swelling and pain in several joints, including usually 2 or 3 fingers.

Moderately severe cases, mostly ambulant. These patients were usually only partly incapacitated and could do certain kinds of work. They invariably presented a multiple arthritis with well-established changes in the hands, wrists, knees and other joints.

Severe cases, only partially ambulant, and capable of performing little or no work.

Relation of Streptococcal Agglutinins to Severity of Rheumatoid Arthritis. The relationship of the severity of rheumatoid arthritis to serum agglutinins for hemolytic streptococci is presented in the following tabulation. The degree of severity (mild, moderate, severe) was established according to the criteria given by Cecil, Kammerer and dePrume.[4]

The majority of our 268 patients suffered from moderately severe rheumatoid arthritis. The percentage having agglutinins for streptococci was practically identical in moderately severe and severe cases; it was lower in those classified as mild.

Relationship of Streptococcal Agglutinins in Rheumatoid Arthritis to Presence of Subcutaneous Nodules and to Psoriatic Arthritis. Subcutaneous nodules were found in 25 of the 268 patients with rheumatoid arthritis (9%). Streptococcal agglutinins were present in the serum of 20 of them (80%).

Psoriasis (arthritis psoriatica) was present in 15 of the 268 rheumatoid patients (5%). Of these, 10 had serum agglutinins for hemolytic streptococci (66.6%).

Relationship of Streptococcal Agglutinins to Sedimentation Rate of Erythrocytes. The sedimentation rate of the red blood cells, as determined by the Rourke and Ernstene method, was studied in 431 patients.

Table 5 shows that in patients with rheumatoid arthritis an elevated sedimentation rate was found more frequently than agglutinins for hemolytic streptococci. However, an elevated sedimentation rate was also present in 22.8% of "normal" controls and in 34% of persons affected with joint diseases other than rheumatoid arthritis, none of whom had agglutinins for hemolytic streptococci. These results indicate that a positive agglutination reaction for hemolytic streptococci is much more specific for rheumatoid arthritis than an elevation of the sedimentation rate.

Effect of Gold Treatment on the Streptococcal Agglutination Reaction. The agglutinin titer for hemolytic streptococci before and after treatment with gold salts was studied in 37 patients suffering from rheumatoid arthritis of varying severity and duration. The gold salt administered was either gold sodium thiomalate (myochrysine) or aurothioglucose (solganal-B oleosum).

The agglutination reaction remained positive in 17 patients, and became negative in the remaining 20, either during treatment with gold salts or after its completion. There was no relationship between the type or amount of gold salts given and change in the agglutinin titer; in some instances the agglutinins disappeared after 300 to 500 mg. of gold salts had been administered, while in others the reaction remained positive after a total gold dosage as high as 13.45 gm. There was, however, some relationship between the changes in the agglutinin titer and the severity of rheumatoid arthritis, its duration and the results achieved with gold therapy.

which the agglutinin titer had become negative was found in mild and early forms of the disease and in those who had shown the most favorable response to gold therapy, an attempt was made to determine if the results obtained could be considered as "specific" for the treatment given. Accordingly, 24 cases who had not received gold therapy were analyzed. These patients received various forms of treatment, such as vaccine therapy, bee venom or physiotherapy. The results in this group were almost identical with those of patients who had received injections of gold salts. Seventy to 80% of the mild and early cases, as well as of those

TABLE 5.—COMPARISON OF TITERS OF STREPTOCOCCAL AGGLUTININS AND SEDIMENTATION RATE OF ERYTHROCYTES UNDER NORMAL AND PATHOLOGIC CONDITIONS

Clinical diagnosis	No. of cases	% having agglutinins in serum dilution of 1:160 or higher	% with C.S.I.* over 0.5
Rheumatoid arthritis:			
"Late"	175	65.6	90.9
"Early"	76	46.1	76.4
Total	251	59.7	86.5
Subacute infectious arthritis	6	50.0	83.4
Ankylosing spondylitis (Marie-Strümpell)	15	6.6	86.7
Osteoarthritis	86	1.1	42.4
Various other joint diseases	44	0.0	34.1
Rheumatic fever	7	0.0	85.8
Normal controls	22	0.0	22.8
Total	431		

* C.S.I. = Corrected sedimentation index.

Of the 37 gold cases studied, 7 had a mild form of rheumatoid arthritis and in 6 of them the agglutinin titer became negative during gold treatment (86%); but of the remaining 30 moderately severe or severe cases only 14 lost their positive agglutination reaction (46%). Similarly, 10 of the 13 early cases (77%), but only 10 of the 24 late cases (41%), became negative on gold therapy. Finally, in 12 of 16 patients (75%) who showed remission or marked improvement the agglutination reaction became negative, while only 8 of 21 (38%) who showed little or no clinical improvement during treatment with gold salts lost the agglutinins for hemolytic streptococci.

Since the highest percentage of cases in showing marked improvement, lost their agglutinins; but in only 30 to 40% of patients with severe or late arthritis, and of those with little or no clinical improvement did the agglutination reaction become negative.

Discussion. The results obtained in this study indicate that the centrifugation method offers optimal conditions for the detection of streptococcal agglutinins in the serums of men and of animals. This procedure permits the titration of the antibody content within a few hours after the withdrawal of the blood, and it yields a sharp end reaction even in high dilutions of serum. This is in agreement with similar observations on the detection of pneumococcal agglutinins.[11]

Living streptococci and those killed by heating or by the addition of formalin were agglutinated equally well. This corroborates the observations of Dawson, Olmstead and Boots.[9]

In order to avoid non-specific agglutination reactions so frequently observed at lower temperatures, the agglutination tests with living streptococci were always done at 56° C. (incubation method); with the centrifugation method the reaction with the heat-killed antigen was carried out at room temperature (24 to 26° C.).

In studying the optimal conditions of the reaction it was found that the concentration of the antigen must be sufficient to obtain positive reactions over a wide range and at the same time avoid the occurrence of inhibition zones. This is in agreement with the observations by Dean and Webb.[10]

In this series the incidence of streptococcal agglutinins in the serum of 268 patients with rheumatoid arthritis was 60.4%. The incidence was higher (66.3%) in late cases than it was in early cases (46.1%). These results agree with previous reports by Dawson *et al.*[9] and by Short *et al.*,[22] who also found that streptococcal agglutinins occurred in early cases approximately one-half as frequently as in late cases.

Streptococcal agglutinins were found in 30% of cases of subacute infectious arthritis and in 25% of patients with scarlet fever. The incidence of streptococcal agglutinins was very low or nil in the other clinical groups, which included osteoarthritis, ankylosing spondylitis, rheumatic fever, and normal controls. These results are in agreement with those obtained by previous investigators.

A definite relationship was found between the incidence of the agglutinins in rheumatoid arthritis and the severity of the disease. Mild cases had agglutinins in the serum in 46.3%; this figure increased to approximately 66% in more severely affected patients. These results are in accord with the observations of Nicholls and Stainsby,[21] who reported that the average agglutinin titers in patients with advanced joint lesions were higher than in those with less involvement. The incidence of streptococcal agglutinins was particularly high (80%) in patients who had subcutaneous nodules, the presence of which usually indicates a rather severe form of rheumatoid arthritis.

There was some relationship between the rate of sedimentation of the red blood cells and the incidence of serum agglutinins for hemolytic streptococci in rheumatoid arthritis, but this correlation was not absolute; frequently the sedimentation rate was elevated and no agglutinins were found; in other instances agglutinins were detected while the sedimentation rate was normal. Similar observations have been made by Dawson, Olmstead and Boots,[9] by Keefer, Myers and Oppel,[18] by Blair and Hallman[2] and by Short, Dienes, and Bauer.[22] High sedimentation rates were also observed in various other joint diseases and even in normal controls. This indicates that the agglutination reaction for streptococci is more specific for rheumatoid arthritis than the sedimentation rate of the erythrocytes.

Treatment with gold salts of patients with rheumatoid arthritis was frequently followed by diminution or disappearance of the agglutinins for hemolytic streptococci. This was noted particularly in patients who showed a good respones to gold therapy. However, the reduction of the antibody titer was not limited to patients who had received gold therapy. Similar observations were made in patients who had shown favorable response to other forms of therapy. On the other hand, gold did not interfere with the production or with the persistence of streptococcal agglutinins. It may be concluded, therefore, that gold does not exert a direct influence upon the agglutinins. In other words, gold does not affect directly the production of agglutinins, nor does it play an immediate rôle in their disappearance except in those cases where remission or great improvement occurs.

Summary and Conclusions. 1. Optimal conditions for the detection of agglutinins for Group A hemolytic streptococci in the serum of patients suffering from rheumatoid arthritis have been studied. The most rapid and satisfactory reactions have been obtained by centrifugation of the test tubes containing the antigen-antibody mixtures at room temperature.

2. The incidence of streptococcal agglutinins in 268 patients with rheumatoid arthritis was 60.4%. It was higher in late cases (66.3%) than in early cases (46.1%). In both early and late cases, the percentage of positive reactions was higher in the severe cases than in the mild ones.

3. In patients with rheumatoid arthritis there was a rough parallelism between the percentage of positive agglutination reactions for hemolytic streptococci and the sedimentation rate of erythrocytes.

4. Treatment with gold salts did not exert any specific influence on agglutinins for hemolytic streptococci. Diminution or complete disappearance of the agglutinins was observed in a majority of rheumatoid patients who showed a remission or marked improvement, whether they received gold therapy or some other form of treatment.

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PROGRESS
OF
MEDICAL SCIENCE

DERMATOLOGY AND SYPHILOLOGY

UNDER THE CHARGE OF

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TUMORS OF THE SKIN

PART I.—A REVIEW OF RECENT LITERATURE,*

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THE skin, with the exception of the eye, is unique in that its exposed position subjects it to numerous hazards of the environment and also because its lesions are easily accessible for study and treatment. Failure to eradicate cutaneous neoplasm, with the exception of malignant melanoma, is usually the result of improper therapy or neglect by the patient or his physician to start treatment promptly. On the other hand, because of the various anatomic structures in the skin, the new growths and nevi are of many types and when more than one structure proliferates simultaneously, the result is a picture of great complexity. In epithelioma alone, tumors may be derived from the surface epiderm, the appendages (hair follicle, sebaceous gland, sweat gland and nail bed) and abnormal proliferation. About 18 years ago Weidman[324] very ably summarized histologic evidence illustrating the capacity of human epiderm (developed perhaps phylogenetically) to regenerate so vigorously that it may simulate cancer. We do not intend to review all the factors involved in the development of benign and malignant cutaneous tumors, but shall present a proposed classification of the numerous neoplastic (and some nevic) lesions of the skin and a discussion of the recent advances in the knowledge of the character and pathogenesis of a number of the tumors of the skin.

In a survey of this sort a certain amount of imbalance in presentation is inevitable. Lesions with clear-cut pathogenesis may receive little attention although, from the clinical standpoint, they are relatively more important if only because of their numerical incidence. On the other hand, rare but little understood entities may receive more attention than their rare occurrence would seem to merit. In any event, our intention is to present sufficient of the more informative literary references for one to have a convenient basis from which to launch further study.

Certain authors have contributed widely to our knowledge of cutaneous tumors. Their names will appear frequently in connection with their individual contributions.

Pomeroy[234] has offered a classification of tumors which has the endorsement of

* The second part of this review, together with the references for both parts, will appear as the Progress article for this department in the October issue.

Ewing.[1] The section on Cutaneous Tumors is herewith presented not as an entirely acceptable codification but to indicate graphically the extensive scope of the subject.

Tumors of Skin. The nomenclature of skin tumors is the result of an independent evolution and does not conform with the broader views of the nature of tumors recognized in the field of general pathology. To bring the nomenclature of skin tumors in closer accord with the general nomenclature of tumors, the following outline is suggested:

I. Epithelial Tumors.
- A. *Benign Tumor.*
  1. Papilloma.
  2. Sebaceous adenoma.
  3. Sweat gland adenoma.
  4. Epidermoid cyst ("implantation cyst," usually traumatic, may be congenital) (Mason).
  5. Dermoid cyst.
  6. Sebaceous cyst.
  7. Sweat gland cyst.
- B. *Malignant Tumor.*
  1. Basal cell carcinoma.
     (*a*) Common basal cell carcinoma.
        1. Proliferative type.
        2. Destructive type (rodent ulcer).
     (*b*) Epithelioma adenoides cysticum of Brooke (probable origin in hair follicle or sebaceous gland).
     This should be distinguished from adenoid cystic carcinoma (Spies); which may be cutaneous or non-cutaneous, and in the latter situation is usually malignant.
     (*c*) Cylindroma (a nevus arising from embryonal rest).
  2. Squamous cell carcinoma.
     (*a*) Well differentiated.
     (*b*) Partially differentiated.
     (*c*) Undifferentiated.
  3. Mixed basal and squamous cell carcinoma.
  4. So-called "precancerous" dermatoses.
     For many investigators who believe that they have seen Bowen's and Paget's disease begin as true cancer cells, these affections should be classified as cancer (McCarthy).
     (*a*) Paget's disease (occasionally in regions other than the nipple).
     (*b*) Bowen's disease (dyskeratosis, intracellular edema, numerous mitotic figures, and giant cells).
- C. *Secondary Tumor.*
  Carcinoma of breast and stomach are the most common primary tumors (Willis).

II. Connective Tissue Tumors.
- A. *Benign Tumor.*
  1. Fibroma (including keloid, which is tentatively regarded as neoplasm by most investigators).
     Histiocytoma can usually be differentiated from fibroma only by vital staining with colloidal iron (Senear and Caro).
  2. Myxoma.
  3. Lipoma.
  4. Xanthoma.
  5. Neurofibroma.
     The majority of cutaneous fibromas are now known to originate in the perineurium or the interstitial tissue of the peripheral nerves, and are therefore called "neurofibromas" (Andrews).
  6. Hemangioma (clinically many sub-types: "nevus" flammeus, "nevus" vasculosus, angioma cavernosum and "nevus" araneus).
  7. Lymphangioma.
  8. Hemangio-endothelioma.
  9. Lymphangio-endothelioma.
- B. *Malignant Tumor.*
  1. Spindle cell sarcoma.
  2. Fibrosarcoma.
  3. Liposarcoma.
  4. Neurogenic sarcoma.
  5. Hemangio-endothelial sarcoma.
  6. Lymphangio-endothelial sarcoma.
  7. Kaposi's disease (question as to whether sarcoma or not).
- C. *Secondary Tumor.*
  1. Sarcoma (sarcoma of bone and lymphosarcoma may metastasize to the skin [Willis]).

2. Myeloid leukemia (leukosis).
3. Lymphoid leukemia (leukosis).
4. Hodgkin's disease.
5. Mycosis fungoides (if any case is definitely shown to be a cutaneous manifestation of Hodgkin's disease or of lymphosarcoma, it should be so named).

III. Tumors of the Pigment-forming Tissues.

It is quite generally accepted that the nevus cell is the parent cell of the melanoma, but the origin of the nevus cells is still a controversial question. In both the benign and malignant forms of tumors arising from pigment-forming tissues, the amount of pigment is extremely variable. The designation of a tumor as a nevus or melanoma is dependent upon the type of cell rather than upon the presence of pigment.

A. *Benign Tumor.*

1. Nevus (there are many varieties, including pigmented and non-pigmented, angiomatous, hairy, fibrous and papilliferous forms).

B. *Malignant Tumor.*

Malignant melanoma or melanoblastoma.

C. *Secondary Tumor* (malignant melanoma may metastasize to the skin [Willis]).

IV. Glomus Tumor.

Neuromyo-arterial Tumor.

This is most common in the nail bed but may be found in other locations. It was formerly diagnosed as angiosarcoma, perithelioma or painful subcutaneous tubercle.

Any classification of cutaneous tumors is limited and not satisfactory because of our imperfect knowledge of the nature of many of the lesions. This classification contains tumors under headings, as well as comments regarding the nature of some of the lesions, which are not acceptable to all. In addition, there are certain omissions such as mixed tumor, for example. In this review special attention will be paid to some of the epithelial tumors, benign and malignant, to some of the connective tissue tumors and "pigment-forming tissue tumors," but we will not consider the tumors often spoken of as the lymphoblastomas.

Tumors of the Sebaceous Glands. Tumors of the fat glands of the skin are either benign or malignant. Benign tumor-like enlargements of the sebaceous glands have a histologic appearance which may not differ appreciably from that of the normal glands. There is considerable confusion and difference of opinion relative to the evaluation of benign neoplastic growths of the sebaceous glands just as is the case in connection with the various glandular structures throughout the body. Woolhandler and Becker[340] in a valuable contribution classified their cases as adenoma sebaceum (Balzer); adenoma sebaceum (Pringle); acquired (senile) adenoma sebaceum; keratotic adenoma sebaceum; nævus sebaceus; nævus pigmentosus et sebaceous. There are other modifications of sebaceous gland growths and recently Arnold[13b] presented the case of a linear unilateral lesion in which the sweat and sebaceous glands were larger and more actively secreting than those in the surrounding skin which he called *nævus seborrheicus et sudoriferus.* Warren and Warvi[322] classify circumscribed lesions according to their clinical characteristics: (*a*) those occurring in old age; (*b*) those appearing at birth and at puberty; (*c*) those associated with other cutaneous and visceral abnormalities forming the syndrome of Pringle's disease.

There is no clear-cut histologic distinction between adenoma; hyperplasia and hypertrophy of the sebaceous gland. In fact, there are some authors who feel that adenoma is rarely a definitive morphologic entity. The abnormality is chiefly one of increase in age, number and location of glands "with minor aberrations such as absence or atrophy or basal cells, variations in the tendency for the central cells to degenerate, or absence of ducts. Atrophy of the lesions is not uncommon; some may become fibrotic; others may entirely disappear" (Warren and Warvi).

Although there are hyperplastic and hypertrophic changes in the sebaceous

glands as a result of chronic irritation (rhinophyma), these can hardly be classed as neoplastic.

Senile sebaceous adenoma ("Caspary's sebaceous adenoma") is the name employed for a relatively common cutaneous lesion, appearing on the face of seborrheic persons after puberty. The fully developed typical lesions are yellowish, irregularly round, flat-topped, frequently umbilicated papules. They are usually found on the forehead and nose but may occur elsewhere on the face. They may be single or multiple. Nomland[212a] noted that they varied from less than 12 to more than 50 in number. Microscopically the chief change is hyperplasia of the sebaceous gland. There is usually an associated dermatitis of the involutional senile type. The exact nosologic position of this tumor is unsettled. Woolhandler and Becker in their review concluded that there is little support in the literature for the concept of senile sebaceous adenoma. Gilman[98] objected to the designation of the lesions as either nevi or adenomas. He pointed out that the glands composing the tumors are normal except for their complexity and size, that their arrangement is orderly and that they are all connected to follicles. He proposed the name adenomatoid sebaceous hyperplasia and believed that *Demodex folliculorum*, as a source of chronic irritation, was responsible for the process. The cause of the condition is still undetermined. Woolhandler and Becker, from their studies, believe a tumor is nothing more than simple adenomatosis (hyperplasia) and an acceptable designation for it is acquired sebaceous adenomatosis.

Adenoma Sebaceum (Balzer). Balzer and Menetrier[19] were the first to use the term adenoma sebaceum for a process consisting of multiple tumors symmetrically distributed on the face, neck and scalp which appeared before puberty and continued to develop until the time of observation. Clinically, the lesions were yellow to pink discrete papules with white points resembling milia on their surfaces. Microscopically the lesions contained cellular nests with a tendency toward lobular arrangement and cystic structure. Some of these lobules were connected with normal sebaceous glands. The cells constituting the tumor masses resembled those of the basal cell layer of the sebaceous alveoli, which in general did not undergo normal fatty changes. Around many of the cysts a gradual transition from the ordinary tumor cells resembling more closely those seen in the centers of normal sebaceous glands were observed. Balzer and Menetrier concluded that the tumors were true adenomas originating in the pilosebaceous apparatus and the cyst contained sebaceous material. Balzer and Grandhomme[18] presented an analogous case in 1886. Since these reports, other cases purporting to be examples of the Balzer type of adenoma sebaceum have appeared in the literature. As a result of the various contributions three schools of thought have emerged as regards the nosologic position of this dermatosis: (1) it is a sub-variety of Pringle's sebaceous adenomas, the tumors being relatively avascular; (2) it is a sub-variety of Pringle's adenoma sebaceum with the lesions showing changes in the hair follicles; (3) it is epithelioma adenoides cysticum, a variety of multiple benign cystic epithelioma. Woolhandler and Becker consider the first two of these as untenable and subscribe to the idea that adenoma (Balzer) belongs in the group of multiple benign cystic epithelioma (*cf.* Ingels[132]).

Adenoma Sebaceum (Pringle). Otherwise known as tuberous sclerosis and epiloia, Pringle's adenoma sebaceum, is a syndrome represented by various combinations of cutaneous tumors, visceral tumors, tuberous sclerosis, epilepsy and mental deterioration. The classical picture occurs in the syndrome known as epiloia recently described in detail by Butterworth and Wilson,[46] Good and Garb,[104] and Noon and Williams.[213] In this state which may occur in from 0.1 to 0.5% of the population of United States institutions for epileptics and feeble-minded (Noon and

Williams), three cardinal features are present: adenoma sebaceum, epilepsy and mental deterioration, with or without visceral tumors.

Description of the cutaneous lesions in the Pringle type of adenoma sebaceum is given by Woolhandler and Becker as follows:

> They "occur invariably on the face, especially in the center, or so-called rosacea area, namely, the forehead, cheeks, nose and chin. They are always bilateral and roughly symmetric and vary considerably in number. They are most numerous in the nasolabial folds and on the adjoining part of the cheeks and nose. The lesions are papules or nodules, varying in size from that of a pinhead to that of a bean. Coalescence may occasionally occur, but as a rule the tumors are discrete. Their color varies from that of the normal skin to yellowish white, yellowish or brownish red, the color representing roughly the predominant tissue constituting the tumor. Telangiectases are a common accompaniment, occurring on the surface of the lesions and between them."

Histologically Pringle's adenoma sebaceum shows a variable picture in different cases as well as in the same patient. The basic change is hyperplasia of not only sebaceous glands but blood-vessels and connective tissue as well. The sebaceous gland hyperplasia is indicated by an increase in number and a more superficial location of the glands plus an increase in number of cells of the basal cell type to several layers instead of the usual single layer. Frequently the latter is the only evidence of hyperplasia. The glands retain their normal structure and the individual cells are normal in size and are not hypertrophied. In addition, the glands attached to hair follicles, their normal location, are also seen, as a rule, to be hyperplastic. The lesion is not encapsulated. Woolhandler and Becker believe the name adenoma sebaceum can be reasonably applied to these lesions in accordance with Ewing's[87] physiologic rather than strictly morphologic concept of adenoma.

Certain cutaneous lesions occur in association with adenoma sebaceum (Pringle). They consist of small flat fibroma, nevi, papulo-epitheliomus (skin tags), warts, pigmented and depigmented macules, so-called shagreen patch and periungual and subungual lesions (Butterworth and Wilson). Warren and Warvi[322] mentioned that, in accordance with numerous authors, Von Recklinghausen's disease may be suggested by the presence of cutaneous pigmentation, nevi, papillomas and fibromas. In the visceral organs a variety of tumors, fibromas and cysts may be found. Although mental defects, psychoneurotic symptoms and lesions, such as retinal gliomas, tuberous sclerosis and local agenesis of the brain make up part of the syndrome in many cases, in a large number no mental defect is detectable and, in fact, some patients are intellectually above the average. Gunther and Penrose[113,228] showed that a single dominant gene is probably the main causative factor and in all probability 25 to 50% of all cases are directly due to a mutation in one or another parent.

Treatment of adenoma sebaceum is purely cosmetic. Destructive measures by various means are necessary. Roentgen therapy plays but little part in the treatment.

The variety of findings (widespread congenital abnormalities) which may be found in a patient with Pringle's disease is illustrated by the patient observed at autopsy by Warren and Warvi. The significant findings in this case were: (1) Hyperplasia and hypertrophy of sebaceous glands. (2) Neurofibromata of the skin. (3) Congenital cystic disease of the lungs with pneumothorax on the left. (4) Tuberous sclerosis associated with cystic softening of the left lenticular nucleus. (5) Ovarian leiomyomata. (6) Mesenchymal rests of the kidneys and retroperitoneal tissue. (7) Recent hemorrhages into renal calyces.

Keratotic Adenoma Sebaceum. Among their cases Woolhandler and Becker had one which clinically resembled senile keratosis, but microscopic examination re-

vealed acquired sebaceous adenoma with epidermal hyperkeratosis.

Adenoma of the Sebaceous Glands. Both Warren and Warvi and Woolhandler and Becker admit the possibility of adenoma of the sebaceous glands. The latter authors report a case in which they felt the diagnosis of sebaceous gland adenoma was justified. The former writers state that they consider the term adenoma as appropriate for certain solitary tumors of the sebaceous glands such as were reported by Carol[51] and by others from the Meibomian gland and other locations. The tumors which Warren and Warvi accept as adenoma are rounded nonulcerated, firm, and consist of a circumscribed overgrowth of sebaceous cells producing masses larger than the usual glands and less regular in shape. These glands frequently lie close to the epidermis rather than in the mid-corium. The lesion suggests an expansile growth of the peripheral portions of the gland. The cells in the center are more normal; those in the periphery stain more deeply, partly as a result of less and more finely divided liposa and partly due to somewhat larger and more hyperchromatic nuclei. Mitotic figures are frequent, numerous or absent. Malignant degeneration of adenomas are frequent. Two of Warren and Warvi's patients with sebaceous carcinoma apparently developed from adenoma.

Nævus Sebaceus. In 1895 Jadassohn[133] first described a prenatal type of adenoma sebaceum which is known as nævus sebaceus. He differentiated this from the various types of adenoma and considered it a nevoid growth composed partly or entirely of sebaceous glands of normal structure. This subject was reviewed by Robinson[251] in 1932 who collected reports of only 35 cases and cited 4 of his own. Savatard,[259] Woolhandler and Becker have carefully brought the subject up to date and believe it is produced by prenatal hyperplasia of sebaceous glands, is entirely benign and is of cosmetic interest only. It may occasionally be associated with nævus pigmentosus. According to Savatard this lesion throws no light on the etiology of sebaceous carcinoma. It may be completely eradicated by excision or electrodestruction.

Nævus Pigmentosus et Sebaceus. Adenomatous sebaceous glands may at times be observed in association with other abnormalities which have often been linear nevi. Woolhandler and Becker describe a case illustrative of a combination with pigmented nevi.

Carcinoma of the Sebaceous Glands. The subject of the relationship of carcinoma of sebaceous glands to adenoma and hyperplasia has been fully studied in the excellent paper of Warren and Warvi.[322] They believe that the only carcinoma that can be characterized as sebaceous is one which reproduces in some part the characteristics of the normal gland. They found 29 cases among 4000 cutaneous carcinomas. They include 20 cases of supposed carcinoma of the sebaceous gland not included in Beach and Severance's[21] review of the literature. There is nothing striking in the gross pathology that would suggest sebaceous carcinoma. The histopathology, however, is distinctive. The cells and pattern of growth closely resemble the normal glands, but even in the most highly differentiated parts there are certain variations from normal structure. The flattened peripheral cells of the normal gland are absent. Instead, the external layer of cells tends to be slightly basophilic and less heavily vacuolated. Most of the tumors in their series were not so well differentiated. In these there is greater variation in size and shape of cells, the nuclei are intensely hyperchromatic, mitotic figures are more numerous, and the lipoid is in finer globules or absent. The cytoplasm may be eosinophilic or basophilic and sometimes keratinized. The typical structure of sebaceous carcinoma may be discernible only in small foci. The tumors grow slowly and ulcerate late. Although the tumors are often resistant to treatment and may metastasize, the prognosis is good if adequate

excision is made early. Even recurrences may be cured by thorough excision.

Tumors of Sweat Glands. Sweat gland tumors are probably fairly common but are rarely seen in the laboratory because they are seldom removed unless they are unusually large. Gates, Warren and Warvi[97] in their comprehensive review of this subject discuss the following types of change:

A. Hypertrophy, hyperplasia and metaplasia.
B. Tumors of true sweat glands.
   1. Syringoma.
   2. Hydradenoma papilliferum.
   3. Hydradenoma.
   4. Hydradenoid carcinoma.
C. Tumors of specialized sweat glands.
   1. Ciliary gland.
   2. Apocrine gland.
   3. Ceruminous gland.
D. Tumors ascribed to sweat glands.
   1. So-called sweat gland carcinoma of the breast.
   2. Turban tumors.
   3. Mixed tumors.

Hypertrophy, Hyperplasia and Metaplasia. The sweat gland is not prone to show hypertrophy or hyperplasia as a primary change but may do so as a secondary phenomenon in cases of certain benign neoplasma of the skin. The subject of hyperplasia was discussed by Weidman[324] in 1928. In 1923 Stokes[278d] presented the case of a girl, aged 19, with lymphangiomatous and hemangiomatous nevus associated with enormous hypertrophy of the sweat glands and localized hyperidrosis on excitement. Epithelial metaplasia, commonly associated with chronic irritation is only occasionally seen in sweat glands. Walther and Montgomery[315] reported a case of metaplasia of the sweat ducts in the verrucous lesion of the palm of a woman aged 29. The metaplasia, mucinous, did not affect the secreting portion of the glands.

Tumors of True Sweat Glands. The subject of sweat gland tumors is very confused in the literature. Gates, Warren and Warvi[97] state the essential points of controversy in differentiation of sweat gland tumors as: (1) distinction from tumors of other structures; (2) differentiation from hyperplasia of the glands; (3) recognition of tumors developing from the secretory and from the ductal portions of the gland. Their discussion of the literature on these points leads to the statement that the subject is still ill-defined, and on the basis of their experience and the literature they recognize four distinctive types of tumors of sweat glands: (1) syringoma; (2) hydradenoma papilliferum; (3) hydradenoma; (4) hydradenoid carcinoma. This terminology is suitable for purposes of our discussion.

Syringoma. This tumor has been designated by a variety of names: Syringoma or syringadenoma (Fiocco, Dohi, Eller, Gans, Unna); syringocystadenoma (McCarthy, Sutton and Sutton, Török); syringocystoma (Neumann, Finnerud and White); hydradénomes eruptif (Jacquet and Darier); epithéliome kystique bénin (Jacquet); cellulome épithélial eruptifs (Quinquaud); cystadenome epithélial bénin (Besnier); lymphangioma tuberosum multiplex (Kaposi); hemangio-endothelioma tuberosum multiplex (Jarisch); spiradenoma (Ewing); nævi cystepitheliomatosi disseminati (Pernet).

Clinically, the lesions affect females, especially at puberty, but may appear first in middle life. They are small, and multiple, but may be occasionally single. The individual lesion is somewhat elevated smooth, colorless, or slightly discolored. The chest and axillæ are especially affected in contrast with epithelioma adenoides cysticum which particularly affects the center of the face. The tumors are radiosensitive. Histologically, they present a typical picture consisting of epithelial groups (dilated cystic sweat ducts) scattered haphazardly throughout the corium without appreciable disorganization of the general architecture of the dermis. The individual unit is a relatively short, narrow, sometimes branching strand of epithelial cells about the diameter of a normal coil duct, which it closely re-em-

bles. Cystic expansion, apparently the result of degeneration, adds to the similarity. The absence of myo-epithelium suggests origin from the ducts rather than the coils. The cysts are lined by cuboidal or flattened cells and contain clear fluid or hyaline, or, rarely, horny material. There may be a distinct basement membrane. The sweat glands adjacent to the tumor may be normal, absent or abnormal. Ingels reported a case with histologic features of both syringoma and epithelioma adenoides cysticum. It is commonly believed that the tumor originates from embryonic sweat glands.[68,242,332]

Weidman and Besançon[325] regarded their case as one of true sweat-gland adenoma, rather than nevus. They could not demonstrate any connection with differentiated sweat glands and raised the question of a possible apocrine gland origin. This concept has been reëmphasized by Homma and Escher.[122] Ormsby and Montgomery[216] have seen no connection between the apocrine glands and the syringoma. They have seen connections with normal eccrine sweat ducts but not with mature eccrine glands. Gates and her co-workers[97] observed only 1 case of syringoma in their material.

Hydradenoma Papilliferum. In the general literature of tumors, the name for a papillary growth of variable structure is hydradenoma papilliferum. In the dermatologic literature, however, this type of lesion is known either as nævus syringadenomatosus papilliferus (Werther) or as nævus syringocystadenoma papilliferus. This usually solitary and slowly growing tumor occurs on the genitalia, perineum, thighs, and face and scalp. The clinical characteristics of the disease are well described by Frieboes,[94] as follows (cited from Sachs and Lewis[257]): "The favorite sites are the shoulders, the axillæ, the genito-inguinal and surrounding regions and the hairy portion of the scalp. The lesions are rose-red papules of firm consistency from the size of a millet seed to that of a hemp seed, usually arranged in groups. Owing to their transparent nature, one or more vesicle-like inclusions may often be distinguished; these inclusions are from the size of a pin-point to that of a pin-head and filled with clear fluid. In addition, the papules are umbilicated at their summit, being similar to lesions of molluscum contagiosum. (Because of this finding, solitary lesions of long duration clinically resembling lesions of molluscum contagiosum may prove to be nevi of the type under consideration.) The papules stand out discretely or form directly confluent plaques. In 1 case (Kreibich) papillary growths were observed on the surface of such a plaque."

Histologically, the sweat glands are somewhat dilated and the sweat ducts cystic in places. The inner surface of the cavity of the duct contains small, villous-like projections. The lining is composed of two or more layers of cells including an inner columnar and outer cuboidal layer. The epidermis is acanthotic; there may or may not be an associated inflammatory reaction. Stokes[278a] reported a reaction suggestive of granuloma pyogenicum. The nature of this lesion is not definitely known. It has been considered as congenital by some. Other associated cutaneous lesions of an inflammatory nature have suggested a reactive process.

The first case of nævus syringadenomatosus papilliferus reported in the United States was that of Stokes.[278a] Recent publications by Nödl[211a] and Sachs and Lewis contribute 3 and 5 cases respectively. We have encountered only 1 case among 2500 biopsy specimens of cutaneous lesions examined in our laboratory. Gates, Warren and Warvi review the entire subject and describe under the heading "Hydradenoma Papilliferum" the various varieties of lesion which have been reported in the literature as distinctive tumors. These lesions are apparently not all the same.

Hydradenoma. Under this designation, Gates, Warren and Warvi classify a solid tumor of sweat glands. According to them, this is more common than all the other tumors of sweat glands together and less frequently recognized as originat-

ing from these structures. It is a grossly discrete, solitary or multiple growth, sometimes appearing in groups, that is found chiefly, although not exclusively, on the face and scalp. It produces a low, mound-like elevation, except on the scalp where it may be pedunculated. The tumor is frequently located in the subcutaneous tissue and lower corium but may involve the entire corium. Rarely it seems to arise close to the epidermis. Ulceration is unusual. The tumor may be of any size, but is rarely more than 4 cm. in diameter. Growth is slowly progressive to a certain limit and thereafter the lesion usually remains of the same size. Histologically, the majority of tumors consist essentially of alveolar spaces embedded in compactly arranged, solid cell masses and strands.

Sutton[287a] presented a rare sweat gland tumor composed of discrete nodules unilaterally disposed on the neck of a woman aged 45. Microscopically it revealed cystic and alveolar structures. Sutton explained this lesion, which he called syringocystadenoma nodularis, as a proliferation of sheath cells of the gland rather than as a proliferation of the secretory epithelium. Cooper and McDonald[62] report a case of adenoma of apocrine sweat glands (hydradenoma) of the anal canals. They believe these tumors are clinically benign (Gates, Warren and Warvi). The nature of hydradenomas is not fully known. They have been considered as arising from hair follicles, and sebaceous glands, as well as from sweat glands and endothelium.

Hydradenoid Carcinoma. Carcinoma of sweat glands has been made the subject of a painstaking research both of the literature and their own material by Gates, Warren and Warvi. A careful study of this portion of their presentation is imperative for anyone desiring acquaintance with this type of carcinoma. Only 6 of their tumors of the sweat gland were frankly malignant. One of them consisted of a lesion around the anus composed of malignant change involving specially the apocrine sweat glands.

Tumors of Specialized Sweat Glands. Tumors of specialized sweat glands, ciliary, apocrine and ceruminous have little clinical importance, and therefore need not be detailed here.

Tumors Ascribed to Sweat Glands. Gates, Warren and Warvi do not recognize the so-called sweat gland carcinoma of the breast as a true tumor of sweat glands but rather as a tumor of mammary epithelium. "Turban" tumors of the scalp, mixed tumors of the skin, seem to be sufficiently unrelated to sweat gland tumors to be discussed separately.

Sheldon[266] described 3 cases of sweat gland tumor in which myo-epithelium had undergone neoplastic proliferation, 1 benign, 2 malignant. In 1 case epithelium and myo-epithelium were involved. In 2 cases only the myo-epithelium represented the main tumor element. It is difficult to classify these lesions.

"Turban" Tumors. These lesions, also known as cylindroma, nevo-epithelioma, adenoides, endothelioma capitis, and sarcoma capitis, are characterized by various-sized tumors occurring chiefly on the scalp. There may be similar but smaller tumors on the glabrous skin. The lesions are round, bluish or pink, and firm and usually do not ulcerate. They persist for a long time and are often mistaken for cutaneous metastases. They are more frequent in women than in men. Sachs and Sachs[258] reported the first case in a Negro. They are histologically characteristic and have a typical arrangement of basal cells in round, oval, or elongated nests, packed closely so that the tumor is in solid lobules. The neoplastic process in the corium is separated from the epidermis by a narrow band of normal connective tissue. The connective tissue around the tumor masses is degenerated into dense hyalinized sheaths. In certain areas there may be poured-in masses of hyaline in the tumor lobules. The origin of the tumor is questioned. Jones, Alden and Bishop[136] consider it of sweat gland

origin; Ronchese,[252a] sebaceous gland; Stillians,[277] surface hair follicle; and Binkley,[32] of diverse origin. From their exhaustive survey, Gates, Warren and Warvi conclude that the turban tumor is not a special histologic entity and may resemble various slowly-growing epithelial tumors of the skin and its appendages. It has been generally recognized that the clinical and histologic characteristics are those of a benign organoid tumor.

Mixed Tumors of the Skin. These lesions, which occur mostly in the salivary glands, have been the subject of study by numerous surgeons, pathologists and dermatologists.[1,15,58,77,79,97,116,153,163,181,203,230,249,261,267]

Mixed tumors are a poorly defined group of neoplasms composed of 2 or more types of tissue and characterized by pleomorphism. They are found in all parts of the body and have been attributed histogenetically to each of the 3 germinal layers. Ectodermally derived tumors most often arise in connection with the salivary glands (the majority are situated in the glands or in close proximity to them). Occasionally tumors morphologically identical with mixed tumors of the salivary glands arise in the skin, in the mucous membranes and in glandular structures other than the salivary glands. They are mostly located in the cephalic region, especially in close proximity to embryonic fissures, the lips, the buccal mucosa, the palate and the lachrymal glands. This rare cutaneous tumor is seen on the scalp, and the face, the forearms, the hands, the thighs, the legs. Moorehead claims more have been reported on the trunk. He reports 4 cases of cutaneous mixed tumors located on the skin of the breast, the nose, the sternum and the ear. This is the first instance of such neoplasms arising in the skin of the trunk to have been reported. Histogenesis of the salivary gland mixed tumors and those of the skin and the breast is the same. Among the possible explanations for these tumors are: true teratomata or slowly-growing epithelial tumors with metaplasia of epithelium and/or stroma.

The pathology of this tumor is especially carefully worked out in the study of Harvey, Dawson and Innes.[116] They define the tumors as adenomas of the serous and seromucous glands, salivary or lachrymal, of undifferentiated and gland-lobular types, prone to mucoid, autolytic, self-destructive change of their component tissues. The cells exhibit epidermoid characters both as basal cells and as squamous ones with intercellular bridges and keratinization. On the whole, the tumors consist of polyhedral or spindle-shaped cells arranged in parenchymatous masses, irregular anastomosing strands or islands of closely-packed uniform basophil cells without indication of keratinization. The nuclei are hyperchromatic and the scanty cytoplasm is acidophilic. Mitotic figures are numerous only when the lesion is malignant. The designation mixed is due to the tendency of the epithelium and the stroma to show hyaline and chondroid transformation. Isolation of epithelial cells tends to give them the appearance of cartilage cells within their capsules. Tumors are usually benign and may recur after removal surgically because of incomplete excision. Occasionally malignancy of glandular or epidermal character may ensue. McFarland (1942) aptly stated that "something more than a simple microscopic examination of a section of tissue will be required before an accurate prognosis of a mixed tumor of the salivary glands becomes possible. At present our methods are no more accurate or scientific than the flipping of a coin."

Mucous Gland Tumors in the Skin. Mucous gland tumors studied by Ginsberg and Reuter[99] are rare. They may occur over any part of the body and even at sites where anatomic considerations would make them unexpected. Ginsberg and Reuter's 2 cases involved the neck and upper part of the chest but the lesions have been found near the ear, in the neck and about the male urethra. Those occurring about the ears, the neck and upper

part of the sternum are usually rests of branchial pouches. Those occurring about the genitalia usually represent disturbance in embryonic development in the closing of the genital groove. Those occurring elsewhere probably arise from sweat glands which undergo metaplasia to correspond to mucous and salivary glands.

Epithelial Cysts. Cutaneous cysts have been classified by Warvi and Gates[323] as epidermal, traumatic, sebaceous, sweat gland, dermoid and follicular. Excellent reports on the subject of cysts, aside from that by Warvi and Gates, dealing with 566 epithelial cysts, are those of Bishop[34] reporting 119 sebaceous cysts; Wein and Caro,[334] traumatic epithelial cysts; Stone and Abbey,[279] 363 sebaceous cysts; Dolce and Clark;[75] New and Ehrich,[207] 103 cases of dermoid cysts; Ehrich,[80] various types of "cutaneous" cysts; Love and Montgomery,[167] on epithelial cysts. Warvi and Gates stated that cysts of the skin may be put into one or another of 3 main groups according to their origin: (*a*) aberrant squamous epithelium, either congenital or traumatic in origin; (*b*) overactivity of glands, resulting from general physiologic forces, external conditions, or from some unknown factor; (*c*) degenerative changes of skin appendages or of benign or malignant epithelial tumors.

The commonest type of epithelial cyst of the skin and all but 10 of Warvi and Gates' 566 cysts fell into this group. They are occasionally the seat of malignant change. Trauma by implantation of epithelium, by altering the structure of cutaneous appendages, or by stimulation of epithelial growth may give rise to cysts. Dolce and Clark report 4 cases of this variety of cysts. Sebaceous cysts may undergo malignant change in as high as 9.2% of cases. Stone and Abbey found 2.2% in their 363 cases, to become malignant. Love and Montgomery, however, do not believe that epithelial or sebaceous cysts should be regarded as precancerous. Hydrocystoma or true cyst of the sweat gland is exceedingly rare. Dermoid cysts are likewise rare. Among New and Ehrich's 103 cases, there were 4 groups: 49.5% arose from the naso-optic groove; 12.6% about the nose; 23.3% originated from the branchial arches in and about the floor of the mouth; 14.6% were miscellaneous groups of mid-line cysts developing during closure at the mid-ventral or mid-dorsal line. Multiple follicular cysts have been described under a variety of names. We feel that they represent multiple sebaceous cysts [Beerman[26]]. This type of cyst is well described by Sachs,[255] Prakken,[237] and Mount.[204]

Multiple Benign Cystic Epithelioma (Epithelioma Adenoides Cysticum). These tumors are relatively common. They are usually multiple, with certain clinical and histologic characteristics and those which are primarily tumors of middle age and may be classed with the non-keratinizing tumors. The various names used for this condition are: benign epitheliomata with colloid degeneration; epithelioma adenoides cysticum; multiple benign cystic epithelioma; tricho-epithelioma papillosum multiplex; acanthoma adenoides cysticum; hydradenome eruptif; multiple cystic symmetric nevi; tricho-epithelioma papillosum with syringocystadenoma; cystic basocellular epithelioma; nævus follicularis; Brooke's tumor; adenoid cystic epithelioma. Excellent reviews on the subject are those of Summerill and Hutton,[283] Savatard,[259b] Ingels;[132] Goldman;[103] Traenkle;[304] Nisbet;[210] and Warvi and Gates.[323] This dermatosis begins usually at the age of puberty and is usually hereditary (Goldman) and occurs mostly about the face. It was originally described by Brooke[40] and by Fordyce.[88] They believed that these lesions sprang either from the basal layer of the epidermis or from similar cells in the hair follicles. Traenkle showed that most multiple benign cystic epitheliomas are histologically tricho-epitheliomas and may show great variation in degree of differentiation in respect to hair follicle structure. The more mature forms of the latter structures could be more properly designated hamartoma than epithelioma. Malignancy has

been described following irritation or improper treatment. Warvi and Gates reserve the term epithelioma adenoides cysticum for a benign lesion of hair follicles which is grossly indistinguishable from syringoma and, like it, multiple and familial. The so-called syringomatous type, they believe, is properly classified with the tumors of sweat glands.

Cutaneous Cancer and Precancer. We shall not attempt to detail the numerous studies on the nature and cause of malignancy. Mention of some of them, however, is pertinent to the understanding of the problem of cutaneous involvement. The skin has not been found adaptable to *in vitro* tissue culture studies, both because of difficulties of handling and measurement and also because normal epidermis cannot be carried in tissue culture over long periods without developing cornified layers which eventually cut off the living elements from the surrounding medium (Pinkus,[232a] Cholpin[55]). Höfer[120] has shown *in vitro* that both malignant and normal epithelium of the cornifying type behave alike, so that, as Pinkus[232a] thinks, there is little possibility of keeping these tumors alive and growing for any considerable time (Coman[59a]). Coman has, however, contributed a convincing piece of evidence that there is decreased cohesiveness in cells from squamous cell carcinomas of lip and cervix as compared with normal squamous epithelium or that from a benign tumor. This was measured in milligrams by a method dependent upon the bend produced in a microneedle when a pair of cells was pulled apart. He suggested that this property of the carcinoma cells may be related to a lowered calcium content of these cells.[59b] This lack of cohesiveness of cancer cells had been inferred by Cowdry,[64] who stated that "perhaps decrease in stickiness of carcinomatous cells is a necessary prelude to their invasiveness." Amersbach and his associates,[9,10] utilizing skin respiration as a dermatologic tool, tested the concept of Warburg[316] that an altered kind of internal respiration is characteristic of and, in fact, is the cause of tumors. Their study of a number of precancerous and cancerous lesions of the human epithelium and of the normal epithelium from the same general area showed that in the majority of cases there was a tendency to depression of the O_2–CO_2 respiration of the precancerous and cancerous lesions. This phenomenon, if it could be placed on quantitative basis, might be another method for predicting the really "precancerous" nature of a lesion.

The nature of cancer's origin is a subject of profound debate. Sutton, Jr.,[285a,b] has presented his views on the manner of growth of epithelioma of the skin in two scholarly papers. His thesis is that cancer is a cellular disease. It begins probably in one cell, the progeny of which form a colony of cells, which is the cancer. A solitary cell may possess all the attributes of the cancer state within itself. Histologic evidence shows that carcinoma of the skin in its earliest stages appears to originate in one cell. Neoplastic lesions of the epidermis may be classified in accordance with a slow or swift growth of the altered cells and their strong cohesion, weak cohesion or lack of cohesion. All neoplasms of the skin in which the cells resemble those of the Malpighian layer in undergoing keratinization form a single set, the clinical subdivisions of which are determined by the degree of cohesion and rate of growth. This theory does away completely with the concept of "precancerosis." Small lesions are neoplastic or not. If neoplastic, they may grow slowly and be benign, or grow fast and be malignant. Sutton subscribes to the theory of the origin of cancer in somatic mutation. This theory postulates that genetic alteration of somatic cell may result in the production of a colony which is cancer. The new cells differ from normal ones mainly in the rate of proliferation and capacity for organization. Neoplasms produced by filterable agents are not satisfactorily explained by this theory. His observations consonant with this theory show how epidermal carcinoma begins from few cells

(probably only one cell) and progresses with no fundamental change excepting continued proliferation. In his study of the manner of growth of cutaneous epithelioma, Sutton, Jr., reaffirmed his belief that the evidence presented supports the view that clinically and histologically each spontaneous epithelioma of the human skin behaves like a colony of cells of a new kind and perhaps the new kind comprises the homogeneous progeny of one mutant cell. Montgomery[193g] takes exception to Sutton's classifying epidermal neoplasms on the basis of cohesion of the cells rather than by the widely accepted method of classification and grading of Broders. He does agree with Sutton that the benign or malignant change that may develop in the future cannot be predicted accurately either clinically or pathologically. He also denies that the theory of mutation in the origin of cancer does not preclude the concept of precancerosis but simply tends to explain epithelioma *in situ*. Sutton's (1942) reply to Montgomery leaves the proposition still one susceptible of much polemic debate and little hope for immediate settlement.

As indicated above, the skin is unique (excepting the eye) in its accessibility for study; but it also is so situated as to be influenced by numerous environmental factors from which other organs may to some extent be exempt. Hueper[129b] and Warren[317] have contributed extensively to our knowledge of cancer in its relation to occupational trauma and environment. Environmental cancer is one due to prolonged contact with some cancerigenic agent in the environment. The relationship of a previous exposure to such an agent and the cancer often appearing many years later is frequently overlooked or not understood. Environmental cancers can be divided into 4 main groups according to the type of exposure: (1) cancers caused by agents in the normal environment (due to the continued ingestion of arsenic in drinking water and foodstuffs in certain regions, the solar cancers, etc.); (2) cancer resulting from certain habits (habitual cancer), as for example cancer of lip and mouth in smokers, cancer of the oral lining in betel and tobacco chewers, and cancer of the abdominal skin in kangri users; (3) cancer resulting from use of certain medicinal agents (medicinal cancers), *e. g.*, cancer of the skin after arsenical medication and after exposure to Roentgen rays and radioactive substances; (4) occupational cancer elicited by exposure to chemical and physical agents in the course of regular occupations (most important group).

The chemical and physical agents known to cause cancer (or suspected of causing it) are arsenic, chromates, nickel carbonyl, radium, mesothorium, asbestos, crude and processed mineral oils, pitch, tar, soot, paraffin oil, anthracene oil, creosote, aromatic amino compounds (aniline, naphthylamine, benzidine), benzene, ultraviolet rays, Roentgen rays, radioactive materials and substances from certain parasitic worms. A review of recent advances in cancer research by Lewisohn[158] gives a detailed discussion of carcinogenic substances. We shall refer to those which specifically are of great importance to cutaneous oncology. For general, and easily available recent discussions of the biology and pathogenesis of cancer, the reader is referred to the reports of Cramer[65] and of Spencer.[271] Brief notes on colchicine as a growth stimulator[208] and on the genetic aspect of the enzyme-virus theory of cancer[236] have recently appeared.

Just as the skin because of its location is exposed to various insults, it is an organ demonstrated to have great immunologic powers. Even in the case of cancer, it has been proposed that the production of curable cutaneous carcinoma by irritations which are not carcinogenic to internal organs may save some lives by preventing cancer of the internal organs. For example, Peller and Stephenson,[227] from observations on United States Navy personnel, assumed that cancer of the lip and skin exerts a beneficial (*i. e.*, inhibiting) effect on developing cancer elsewhere. Peller[226] had claimed from occupational mor-

tality statistics of England and Wales (1921–23) that an increase of carcinogenic irritation leads to an increase of cancer in more inaccessible organs. Furthermore, Eisenstaedt[81] noted that although superficial epitheliomatoses exhibited marked tendencies toward multiple cutaneous neoplasia, they do not show tendencies toward multiple malignant tumors elsewhere in the body. The studies of Conrad and Hill[61] and of Shields Warren and Gates,[318a] on the other hand, showed no inverse relationship between mortality from cancer of the skin and lip and mortality from cancer in other sites. On the contrary, Warren and Gates,[318b] in a more recent work involving 1149 carefully studied cases of cancer of the skin, and confirmed by the series of Lombard and Warren,[164] found that there was no justification for recommending the induction of cancer of the skin to protect against the development of cancer elsewhere. In the group with cutaneous cancer there was definitely more cancer of organs exclusive of the skin than would be encountered in a similar population drawn from Massachusetts at large. Cancer of the skin does not protect against the development of cancer elsewhere. As with other types of cancer, cancer of the skin is associated with a greater number of multiple cancers than would be expected on the basis of chance. These new findings sound a note of warning that those dealing with cutaneous malignancy should look for other foci of carcinoma in the body. They also reemphasize the unjustifiable complacent attitude and satisfaction of dermatologists with the superficial significance of cutaneous cancer.

If trauma is a cause of carcinoma, the skin, because of its exposed position, would be especially predisposed. In spite of this, there is no clear-cut evidence definitely to associate trauma and cutaneous carcinoma. Lutz[170] thought that acute trauma could lead to carcinoma (1) in old persons in whom injury in atrophic skin may lead to cancer, (2) in persons burned with hot tar, (3) in those with skin injury and prolonged presence of a foreign body, and (4) young persons whose skin shows no visible degenerative changes. The effect of environment and occupation in the induction of carcinoma has been touched on elsewhere in this review. Shields Warren[317] defined the minimal criteria required to prove causation of traumatic or occupational neoplasms. He accepted a tumor as due to mechanical trauma under the following circumstances: (1) integrity of tumor site prior to injury must be established; (2) the injury must be sufficiently severe to disrupt the continuity of the tissue at the site; (3) the tumor must follow the injury by a reasonable time; (4) the tumor must be of a type which might reasonably develop as a result of the regeneration and repair of those tissues which had received the injury. These criteria seem to us a reasonable set of requirements for critical evaluation of a case purporting to be traumatic in origin. Warren believes that single trauma rarely if ever causes cancer. An interesting example of mixed epithelioma of the back arising from daily application of a phenol and ergot ointment, reported by Stevens and Callaway,[275] may be cited as a reminder of the possibility of traumatic (irritation) cancer from seemingly harmless sources.

The exposed situation of the skin permits of early diagnosis and cure of carcinoma, but contrary to expectation much procrastination by physicians and the laity leads to late cutaneous malignancy with its irreparable if not fatal consequences. This fact is all the more surprising because it is possible, in a high proportion of cases, for a competent clinician not only to diagnose the presence of carcinoma of the skin but actually to indicate the histologic type of tumor. It is true that if treatment is adequate, the histologic verification of the diagnosis is not needed to produce favorable results. Warren, Simmons and Rea[321] studied 829 treated carcinomas of the skin not verified by biopsy. Of these cases, 84% were followed for 5 years. There were 57%

3 year and 48% 5 year cures of all the tumors treated. If the cases lost and dead of intercurrent diseases are counted as cures, the 5 year cures would rise to 84%. If they are entirely excluded, the figures would be 76%. Recurrences occurred in 13% of cases showing primary healing followed 1 year or more. Primary healing occurred in nearly all cases (98%). More than 25% of the deaths from cutaneous carcinoma occurred after primary healing, so that primary healing cannot be taken as a criterion of cure. These authors regarded failures as due to the use of lightly filtered radon applied to the surface in inadequate dosage and feel that Roentgen rays or radium used at a distance might have given better results. They do not feel, in spite of these good results, that the *lack of biopsy alone* was responsible for a better showing in this group than in one previously reported by this group for a biopsy verified series of cases. It is not difficult to understand the good results in Warren, Simmons and Rea's study when one realizes that these authors may unconsciously have made accurate diagnosis clinically in a high proportion of their cases and instituted therapy accordingly. That a high degree of accuracy in diagnosis may be attained by competent observers (not casual observation by the average practitioner) is indicated by the well-controlled study of Torrey and Levin,[301] who noted that the clinical diagnosis of epithelioma was found to be correct for 90% of the lesions, the clinical differentiation between basal and squamous cell epitheliomas was correct for approximately 75%, and 15% clinically diagnosed as benign were found to be epitheliomas. In spite of this apparently easy clinical differentiation, we agree with Warren and his associates[319] that biopsy of all skin tumors is essential for the establishment of rational treatment of skin carcinomas. It also appears to us, however, that a certain amount of classification of the forms of differentiation of basal cell carcinoma serves some useful clinical purpose in regard to prognosis.

Schrek and his co-workers[262a,b,c,d,263] of Huntington Memorial Hospital of Boston and of the Pondville Hospital, Wrentham, Mass., and the Hines Hospital, Hines, Ill., have furnished the literature with comprehensive data on cutaneous carcinoma. This series of articles gives a detailed analysis of: (1) the similarities and differences between basal cell and epidermoid carcinoma; (2) the characteristics of value in differential diagnosis; (3) the efficacy of treatment; (4) the value of grading; (5) the racial distribution of cancer.

Among 581 cases of cutaneous carcinoma the median duration of basal cell carcinoma (3.5 years) was much greater than that of epidermoid carcinoma (1.2 years). The median sizes of the two types of tumor were, however, the same (1.9 cm.). Size, not duration, of the tumor prompted the average patient to seek hospital treatment. At the time of hospitalization the median age of patients was 64.2 years for those with basal cell lesions and 68.2 years for those with epidermoid carcinoma. The median age at time of onset was 57.3 years, and 66.2 years for basal and epidermoid carcinomas respectively. Basal cell lesions develop, therefore, in younger persons than do prickle cell lesions. The findings as to median durations and median ages at time of hospitalization and at time of onset were confirmed by a series of 495 cases of cutaneous carcinoma at the Pondville Hospital. The patients were on an average somewhat older than those of the Huntington Memorial Hospital.

Innate malignancy (the degree of deviation of the tumor from the prototype) of basal cell and epidermoid carcinoma as measured by the median growth rate and the percentage of tumors metastasizing and clinical malignancy (hazard of the tumor to the life and health of the patient) indicate that epidermoid carcinoma is about 3 times as malignant as basal cell carcinoma. But in spite of its low malig-

nancy basal cell type recurs in as high a percentage of cases as the epidermoid type.

The degree of innate malignancy of cutaneous carcinoma may be measured by: (1) the amount of anaplasia of the tumor cells; (2) the growth capacity of the tumor; and (3) the capacity of the tumor for metastasis. Broders'[39] classification is rated as of theoretical interest and clinical importance by Schrek but of limited scope of application, since its usefulness is confined to comparison of tumors arising from a common prototype. It is common experience of pathologists to have the same tumor graded variously by different observers and indeed for the same block to show various grades of activity. Broders, however, regards his method of grading as of value in treatment and prognoses. Casey[52] measured malignancy by means of the mitotic index which Schrek considers an indirect method of determining the growth capacity of a tumor. Schrek advises the use of the growth rate as a measure of growth capacity. This can be applied in the comparison of tumors arising from different prototypes as to innate malignancy: Wilson[336] studied 3221 cases of epithelioma of the lip and skin to correlate the rate of ulceration with such factors as grade of malignancy of the lesion, type of treatment and age of the patient. Of these cases, 793 had been previously used by Broders as a partial basis for grading of cancer and 268 cases of basal cell cancer had been reported by him. In cases of squamous cell epithelioma, the rate of ulceration was found to be directly proportional to the grade of malignancy except with lesions of Grade 4, which were found to ulcerate at a rate between those of Grade 1 and Grade 2. Previously treated epitheliomas were found to ulcerate more rapidly than those which had not been treated. In recurrent epitheliomas, the rate of ulceration was found to be most rapid in the growths previously treated with pastes and salves. Ulceration was more rapid in persons over 56 years of age than in younger individuals. The question of metastasis as an index of malignancy is affected by other factors than innate malignancy. These include character of the blood supply, the lymph drainage, site of tumor and trauma. MacCormack,[171] for example, found that among 108 cutaneous carcinomas, 31 extended to the lymph nodes. This was less than is the case for lesions of the mucous surfaces. Schrek[262a] indicates that the malignancy of a tumor from the clinician's viewpoint is likewise affected by a number of factors. The chief of these is innate malignancy, but location and type of therapeutic intervention are of paramount importance. Clinical malignancy is measured, as a rule, by the percentage of 5 year cures, by duration of life in treated and untreated patients, by survival curves, by life expectancy curves, percentage of patients with recurrences and percentage of patients dying with the malignant growth.

Epidermoid carcinoma has a tendency to be distributed to the ears, the hands and the lower part of the face, in order of frequency. Basal cell carcinoma prefers the upper part of the face, the nose and the ears. Both types occur more frequently in males than in females. This is especially true for tumors of the ears. Tumors of the scalp, trunk and legs were more frequent in the female. Of Schrek's tumors of the scalp, trunk, arms and legs, 18% developed in preëxisting scars which were produced by such injuries as burns, lacerations, surgical operations and ulcerations. If scarred skin is more susceptible to carcinoma, it is evidence of the possibility that a single traumatic injury may eventuate in carcinoma. About 16% of epidermoid carcinomas metastasized to the regional lymph nodes. This was not appreciably conditioned by the site of the tumor.

Cutaneous epitheliomatosis is much less frequent in Negroes than in the whites. In the Tumor Clinic of Edward Hines, Jr., Hospital, Schrek[262d] found among 10,857 white and 724 colored male patients with cancer that cutaneous cancer occurred in 19.2% of the white patients and in 2.8%

of the colored group (7:1). Carcinoma of the exposed skin is much less frequent in colored than in white persons, but carcinoma of the covered skin has the same incidence in the two races. In the white race cutaneous cancer is more prevalent in the southern than in the northern states. White men have a higher incidence of cutaneous cancer than white women, but no sex difference was noted in the colored race. A high percentage of cutaneous carcinoma in colored patients developed in a preëxisting scar (none followed a war injury) or in a chronic inflammatory lesion. A low percentage of scars gave rise to an epithelioma. In his study Schrek surveyed the racial distribution of cancer, based on the records of the Hines Memorial Hospital, of the U. S. Public Health Service on the prevalence of cancer, and on the mortality statistics of the United States. Carcinoma of the exposed skin and of the lip, and keratosis of the skin had a very low percentage in the colored. Carcinoma of the covered skin, however, as previously stated, had approximately the same percentage in the colored as in whites. Exposure to sunlight and other climatic conditions is considered the major etiologic factor in carcinoma of the exposed skin in the white race. Scars and chronic inflammatory lesions are, apparently, important etiologic factors in carcinoma of the exposed and covered skin of Negroes and also in carcinoma of the covered skin of the white race. No analysis of the relation incidence of syphilis in the two groups and its relation to cutaneous cancer in the two races was included in this study.

Sunlight and Cancer of the Skin. This subject has been fully reviewed up to 1942 by Beerman and Stokes.[27] Since this summary was made, light as a factor in skin cancer has been emphasized among others by Weiss and Conrad,[331] Hueper,[129a] and Hueper and Figge.[130] Hueper demonstrated that the epidermis of the rat is capable of producing under proper stimulation (ultraviolet rays, arsenic) as great a variety of carcinomas as that seen in the human skin. With Figge he produced circumstantial evidence in support of the hypothesis that porphyrin metabolism associated with the excretion of relatively large amounts of porphyrin by the Harderian glands is one of the factors that influence susceptibility to light induced cancer in rats. The rôle of sunlight as a factor in the production of cancer is mentioned above in the section dealing with the generalities of the cancer problem.

Pseudo-epitheliomatous Hyperplasia. Pseudo-epitheliomatous hyperplasia in chronic inflammation has long been difficult to differentiate from cancer of the skin. White and Weidman[333] emphasized the extent to which it develops histologically at the margins of ulcers. Every gradation up to perfect imitation of epithelioma may occur so that it becomes impossible to distinguish histologically between squamous cell epithelioma and nonmalignant hyperplasia. These authors believe that a diagnosis of carcinoma is not justified unless the infiltration extends to the level of the sweat glands or farther, or when the pathologist has had wide acquaintance with the behavior of hyperplastic epidermis in general. Winer[337] in his review of this subject has summarized the diagnostic characters which have been reported to differentiate hyperplasia from true cutaneous carcinoma. He concluded that the most frequently noticed histologic finding was the edema of the upper part of the cutis and in the epidermis of all the sections which showed pseudo-epitheliomatous hyperplasia. The edema caused vacuolization of the intercellular spaces in the lower epidermis and disintegration and vacuolation of the epidermal cells in the upper epidermis. Although the edema was diffuse, the pseudo-epitheliomatous proliferation was, as a rule, localized to a single area. Therefore, the factor of nutrition must be considered as being a possible cause of the hyperplasia. This epithelial change has been noted in a number of cutaneous diseases among which are: granulomas; tuberculosis (scrofuloderma and lupus vulgaris);[144,190,309] syph-

ilis;[150,302,333,337] deep ringworm (blastomycosis; sporotrichosis; actinomycosis);[121,196,333,337] iododerma[196] and bromoderma;[101] ulcers,[333,337] traumatic ulcers,[155] verrucous lesions;[105] molluscum contagiosum;[324] multiple pyoderma.[185]

Diagnosis of pseudo-epitheliomatous hyperplasia may be facilitated by identification of histologic features of the associated dermatosis. For example, in syphilis and tuberculosis the characteristic changes in the cutis are helpful in ruling out epithelioma. The deep fungus infections have fairly characteristic histologic pictures. For example, blastomycosis is identified by epidermal abscesses and the causative organisms. Verrucæ and condylomas may offer real difficulty. The hyperkeratosis and parakeratosis, the extreme regularity of the acanthotic process and the intact basement membrane are the differential points. Winer emphasizes that a spontaneous healing in "epithelioma" means pseudo-epitheliomatous hyperplasia.

Precancerous Dermatoses. This term is used loosely by dermatologists to include dermatoses with an incidence of epithelioma no greater than should be expected if certain environmental and other factors, all of which predispose to cancer, are considered, *viz.*, age, senile changes, light sensitivity, chronic irritation, trauma, etc.[216] Some believe the name should be confined to true but rarely encountered cases of Bowen's disease, senile keratosis, arsenical, tar and Roentgen ray or sunlight keratosis and to leukoplakia. Various other diseases, including syphilis, are not classed as precancerous. The so-called precancerous condition is not necessarily represented by an epithelial hyperplasia; in fact there may be epithelial atrophy as in radiation dermatitis, xeroderma pigmentosum and kraurosis vulvæ. The precancerous concept has been criticized by many, since, although there is no clinical malignancy, there is already the histologic picture of squamous epithelioma *in situ*.[82,172b,188,216,286b]

Arsenical Keratosis and Carcinoma. Arsenic is apparently an ubiquitous substance and its widespread use yields countless possibilities for its introduction in the body. The latent interval of many years between administration of arsenic for medicinal purposes and the onset of adverse cutaneous and other organic processes leads to much misunderstanding and to a number of clinical entities which only a thorough knowledge of the effects of arsenic on the skin and other organs will clarify. That this unawareness of the effects of arsenic on the skin in the production of keratoses and cancer is not generally known is evidenced by the numerous times in various tumor conferences that the Reviewer has surprised the assembled specialists by "digging out" a history of arsenic ingestion in what to a dermatologist is an obvious case of arsenical hyperpigmentation and keratoses. Although much literature has accumulated on the arsenic problem, the *modus operandi* of this agent in carcinogenesis is still a mystery. Excellent recent reviews on the general problem and its oncologic aspects are available.[20,36,49,90,193c,201,250]

The lesions of arsenic in the skin are distinctive. The palms and soles especially are affected by clavus-like elevations of varying size (2 to 5 mm.) and elevation. They may be picked out of their keratotic beds. Superficial ulcers or fissures may occur where these horny lesions have been traumatized and carcinomas may develop either in the fissures, the ulcerated or hyperkeratotic lesions themselves. Over the rest of the body, flat, discrete, reddish, sharply delimited, scaling keratoses may occur 0.5 to 10 mm. in diameter with raised pearly borders. Sometimes these lesions undergo malignant change. New lesions resemble psoriatic patches and may, in fact, arise in psoriasis for which the arsenic was given. These keratotic lesions are unlike ordinary senile keratoses in that they are not entirely on the exposed surfaces of the body. They are often associated with varying degrees of hyperpigmentation of the skin resembling "raindrops on a dusty road."

In addition to the cutaneous changes,

some of the patients may show other effects of the arsenical. We have seen, for example, neuritis, hepatitis, with and without ascites, pulmonary metastatic carcinoma, and Franseen and Taylor noted patients with carcinoma of the esophagus, and carcinoma of the pancreas. Neither of these latter lesions were at the sites of excretion and they gave little evidence for the occurrence of arsenic induced carcinoma of the internal organs. Other authors have also found little evidence for internal organ carcinoma of arsenical origin in patients who had received arsenic.

The type of arsenic which produces these late cutaneous changes is usually pentavalent. This was shown by the work of Osborne and his colleagues,[217,218] extending the work of Brünnauer,[41] using a method to precipitate arsenic as trisulfide crystals in tissue sections prepared from arsenical keratoses. He found that the largest arsenic deposits were in the papillæ of the corium and in the basal layer of the epidermis. The coil ducts and glands contained large quantities of arsenic, and considerable amounts were found in the hair follicles. Osborne's group suggested that the mechanism of production of arsenical keratoses seemed to be the speeding up of the keratinization cycle by the deposit of an irritant in the form of arsenic in the upper corium, papillæ and epidermis, and the stimulation of the basal layer in the same manner could probably explain the carcinomas. Trivalent arsenic, on the other hand, had more effect on the vascular elements of the skin and produced a different picture. Unfortunately there is not complete agreement in the literature regarding the reliability of Osborne's method. Tannenholz and Muir[292] believe they had demonstrated similar crystals in controls as in the experimental material. Although in 1941 Becker[23c] as well as Oppenheim[215] cited others in confirmation of Tannenholz and Muir's conclusions, Montgomery and Waisman felt that Osborne's method was valid. Further evidence suggestive of the correctness of the arsenical findings in lesions is the demonstration in hair and nails (especially the slow-growing pubic hair) or arsenic many years after its administration.[117] The mechanism of action of arsenic as a carcinogenic substance is unknown. Montgomery and Waisman believe it can stimulate latent or dormant foci of epithelioma.

Montgomery[193c] found that in 20% or more of the cases of keratosis from arsenic, epithelioma develops, again starting out as squamous cell epithelioma *in situ* with various phenomena of keratinization of individual cells. The histologic changes duplicate those in cases of Bowen's disease and senile keratosis. In addition, there may be a peculiar type of vacuolization of the cells of the epidermis. Anderson[11a] maintained that Bowen's disease and superficial epitheliomatosis are predominantly the result of the ingestion of arsenic.

Milch[189] stated that squamous cell epithelioma with typical pearl formation has invariably been reported by observers of this condition. Franseen and Taylor did not distinguish between superficial epitheliomatosis and superficial epithelioma developing after the ingestion of arsenic and he then reported many cases of basal cell epithelioma which Montgomery[193g] says were erroneously attributed to arsenical medication. Anderson and Franseen and Taylor made no arsenical determinations in their cases. In a later study Montgomery and Waisman[201] state that by proper evaluation of various findings the distinction between epithelioma provoked by arsenic and the lesions of superficial epitheliomatosis and Bowen's disease can be made. In this study the authors believe they have confirmed the concept that arsenical epithelioma is associated with a local concentration of arsenic in the tissues. In contrast with this, the superficial epitheliomatosis usually shows no storage of arsenic. They state that epithelioma provoked by arsenic usually is relatively benign. Our own

experience suggests that this viewpoint is too optimistic.

Treatment of the epitheliomatous lesions due to arsenic should be radical, surgical or electrodestruction. Radiotherapy is inadequate. Developing lesions should be looked for and treated.

Bowen's Disease. In 1912 Bowen presented 2 cases of chronic atypical epithelial proliferation in which there was a solitary lesion composed of lenticular papules which resembled nodulo-ulcerative cutaneous syphilis. He named it "precancerous dermatosis."[37] An early lesion is usually a firm, pale red papule covered with a thickened horny layer and cornified crust. Beneath the crust, the surface might be red and oozing, granular or slightly papillomatous. The plaques may be annular or serpiginous in outline and may extend peripherally and heal in the center. Many of the cases develop squamous cell epithelioma with metastasis and death. It is claimed by some (carefully reviewed by Cipollaro and Foster[56]) that Bowen's disease may occur on the mucous membranes (cornea, Wise[339]). Montgomery,[193a] on the other hand, believes that the term "Bowen's disease" has been used loosely in the literature and that many cases reported as occurring on the mucous membranes are simply cases of squamous cell epithelioma with phenomena of individual cell keratinization. He believes the term should be limited to those lesions resembling Bowen's original description, simulating nodulo-ulcerative syphiloderm, and possibly to the type of multiple lenticular plaques described by Darier and by Fraser.[91] Montgomery had opportunity to study a total of 10 cases of this disease. In all but 1 of them there was a solitary plaque and in all of them the disease was limited to the glabrous skin. These lesions had existed for from 6 to 30 years without history of any kind of progression in the size of the lesions. Contrary to the findings of Anderson,[11a] Cipollaro and Foster,[56] and Arguello, Ferraris and Tello,[12] Montgomery could find no history of arsenic ingestion nor evidence of arsenical pigmentation keratosis or superficial epitheliomatosis. Arguello and his co-workers' case seems to the Reviewer like an ordinary arsenical keratosis with epithelioma.

The histology of Bowen's disease is not diagnostic but is, according to Montgomery (1939), common to all true precancerous dermatoses. He summarized it as being that of a squamous cell epithelioma *in situ* with the phenomenon of individual cell keratinization. Others, however, think the picture is characteristic. Briefly the changes are stated by Anderson (1932) as consisting of hyperkeratosis and acanthosis. The acanthotic epidermis presents large cells with deformed nuclei, multinucleated cells, numerous mitoses, disordered polarity, irregularity in the size and shape of the cells, irregularity of the staining qualities of the nuclei, together with large cells having a vacuolated cytoplasm with granules of chromatin. The corium contains a certain amount of reactive inflammation. Civatte (cited by Marques[177]) depicted 2 histologic types of Bowen's disease one of which becomes in basal cell epithelioma, as reported by various authors (Grutz;[111] Gutman;[114] Goldberg;[102] Szodoray[291]). This is denied by Montgomery. It is, from the beginning, histologically a squamous cell epithelioma.

Many cases of Bowen's disease show penetration of the basal cell layer of the epidermis with resultant invasive squamous (prickle) cell carcinoma. Stout[280d] cites a case to illustrate the possibility of metastasis from Bowen's disease without discovery of gross or microscopic evidence of penetration of the basement membrane.

The cause and origin of Bowen's disease is unknown. It has been considered variously as arising from the sebaceous (Rousset[254]) or sweat glands (Grzybowski;[112] Jorno[137]) or as a delayed nevus (Grütz[111]). The arsenical factor in its etiology has been mentioned above.

The treatment of choice is superficial excision. Radiotherapy is not advised because of the similarity of the histologic

findings to that of early Roentgen ray or radium epithelioma.

Erythroplasia of Queyrat. This "precancerosis" was first described in the American literature by Sulzberger and Satenstein.[282] It had originally been presented by Fournier and Darier[89] in 1893 as *epithéliome papillaire nu.* Queyrat[241] in 1911 designated the process, after much study, as *erythroplasie.* Since then it has been variously known as the *erythroplasie* (erythroplasia), *erythroplakie* (erythroplakia) of Queyrat, or psoriasiform carcinoma of the glans penis.[259c] Numerous cases have been described in the *Archives of Dermatology and Syphilology* since Sulzberger and Satenstein's report. This process so uniformly becomes cancerous and is so prone to metastasis that Sulzberger and Satenstein regard it as a true precancerosis. It occurs chiefly on the penis (glans), glans clitoris, and other parts of the vulva, the lips, the buccal mucosa and rarely the skin itself. Syphilis frequently is found associated with it but it is definitely not the cause. As noted elsewhere, Montgomery regards erythroplasia as a variant of leukoplakia; and states that histologically it is epithelioma *in situ.*

Darier's description of this lesion is quoted from Sulzberger and Satenstein as follows:

> Erythroplasia is found on the buccal mucosa, the tongue, the lips, the cheeks, the glans penis and the foreskin, or on the vulva in the form of a well-circumscribed, erythematous surface, which is velvety and shiny. Its etiology is unknown. Syphilis is not regularly present in these patients. This condition grows very slowly, persists indefinitely and resists all topical remedies; excision or total destruction by cauterization or, preferably, with carbon dioxide snow is necessary, for sooner or later an infiltrating prickle cell epithelioma develops, with early involvement of the regional glands. The differential diagnosis must consider a syphilid, a lupus vulgaris of the mucous membrane, a basal cell epithelioma and, on the genitals, a diabetid (Monilia). In the cases which I know, histologic examination has shown slightly variable lesions. Those which seem to me to be the most characteristic consist of hypertrophy of the rete pegs, without dyskeratosis; these, increased in length and in breadth, are superficially abraded; one finds a moderate cellular infiltration in the upper parts of the cutis. In other cases, clinically identical, one has found dyskeratotic changes which are definitely of the type of Bowen's disease (Hudelo and Cailliau, Richon, on the vulva; G. Barbier, on the mouth), (Sulzberger).

Because of the early malignant change with metastasis, treatment should be radical destruction.

Extramammary Paget's Disease. Paget's disease of the nipple is a relatively well-defined entity both clinically and pathologically and in the last analysis since the majority of the cases (75% Montgomery[193f]) are associated with an underlying carcinoma of the breast, this disease should be considered apart from the cutaneous manifestations as a disease of the breast. Extramammary Paget's disease of the skin has been claimed to be a variant of Bowen's disease, or to represent superficial moist squamous cell epithelioma or metastatic carcinoma (Montgomery, 1937) or as due to the intra-epidermal spread (*a*) of carcinoma of the apocrine glands (and perhaps of other cutaneous glands), (*b*) of carcinoma of mucous membranes bordering on skin, and (*c*) possibly of melanoblastoma (Pinkus and Gould[233]).

In their review of this subject, Parsons and Lohlein[224] state that extramammary Paget's disease has rarely been reported. Weiner[328] in his compilation was able to collect reports of 57 such cases and reported 1 additional case. He finally decided on 15 (including his own) as being true instances of this rare disorder. In 4 of these, the disease involved the male genitalia, in 8 the vulva and in 3 the axilla. Pinkus and Gould, not accepting all of Weiner's cases, reduced the total to 9. Among these 9 there were cases rejected by Weiner and accordingly Parsons and Lohlein are inclined to accept Weiner's 15 cases as the more nearly correct figure. At any rate the number of cases is exceedingly small.

According to Parsons and Lohlein, the term "extramammary Paget's disease" should be restricted to those cases in which the lesion occurs apart from the breast and its covering skin, and is from the standpoint of histology entirely similar to the classic lesion in the breast (*i. e.*, epidermal changes essentially identical with those observed in Paget's disease of the nipple and areola) and in addition carcinoma of the underlying sweat glands. This is essentially the definition of Stout.[280]

Leukoplakia. Leukoplakia is characterized by grayish white plaques on the oral and genital mucous membranes. The sites of predilection for this dermatosis are: buccal mucosal interdental line (made by teeth of upper and lower jaw), the gums above the upper canine teeth and lateral incisors; the sulcus beside the upper and lower gums in the roof and floor of the mouth; and dorsum and edges of the tongue (in lines along the longitudinal axis). The lesions are made up of hyperkeratinized epithelium, covered with an adherent pellicle; they are rough to the touch and usually not tender. There may be a reddened and tender zone in the vicinity. The lesions are very chronic and resist all types of local medicaments. Histologically leukoplakia is characterized by acanthosis with hyperkeratosis. Moderate liquefaction degeneration of the basal cell layer occurs. The dermis shows a cellular infiltrate, in some places perivascular, and with some increase in fibrous tissue. The infiltrate is composed of plasma and mast cells and many lymphocytes and connective tissue cells. The elastic tissue is destroyed. When carcinoma supervenes it usually starts as squamous cell epithelioma *in situ* with features of Bowen's disease.

The best critique of leukoplakia the Reviewer has found is that of Montgomery,[193v] which is as follows:

The incidence of epitheliomatous change in leukoplakia is difficult to ascertain because of the various etiologic factors to be considered. McCarthy justly emphasized that the leukoplakia precipitated by syphilis predominates on the tongue, where atrophic syphilitic glossitis is most frequently the antecedent lesion. Leukoplakia of the buccal surfaces, on the other hand, apparently results most frequently from constant irritation and trauma from smoking or malocclusion. An analysis of different statistics given by MacKee and Cipollaro together with a review of the literature showed that in 20 or 30% of cases leukoplakia of the oral cavity results in malignant change. I can see no difference between leukoplakia or leukokeratosis of the mucous membranes of the mouth and of those of the genitalia, including the vulva and glans penis. Erythroplasia of Queyrat would seem at best only a variant of leukoplakia, being essentially a moist superficial form of the latter. Rëjto's case of erythroplasia of the glabrous skin was an instance simply of moist superficial squamous cell epithelioma. The histologic changes in leukoplakic vulvitis, as distinguished from those of true kraurosis and lichen sclerosis et atrophicus (which has been confused with kraurosis), need not be considered here. I have not been able to demonstrate pathologically any evidence of syphilis in cases of leukoplakic vulvitis. The incidence of epitheliomatous changes in lesions of leukoplakia of the genitalia in my experience has been at least 20%, but if the patients are observed over a long period, as Taussig has done, the incidence of epitheliomatous change may reach 50%. Clinically, as in experimental production of cancer, involution of early leukoplakic lesions in the mouth or on the tongue may be seen after cessation of smoking or the fitting of proper dentures, thus again indicating the reversibility of the process if it has not gone too far.

In contrast with the previously mentioned types of precancerous dermatosis, leukoplakia of the mucous membranes, although frequently starting as an epithelioma *in situ*, may be seen often in the form of an ordinary type of penetrating squamous cell epithelioma, Grades 1 to 4, without much evidence of malignant dyskeratosis or keratinization of individual cells.

Leukoplakic Vulvitis and Kraurosis. Bonney[35] clearly defined the 4 stages of the clinical picture of leukoplakic vulvftis which he and Berkeley[30] had separated from the other forms of vulvitis and named. Kraurosis is another vulvar affection about which there is great confu-

sion. The designation has been used to include many different conditions which have one feature in common, contraction of the vaginal orifice. A clear differentiation between the two processes, leukoplakic vulvitis and kraurosis, which some authors still feel are different stages of the same entity, was made by Graves and Smith[107] as follows:

Leukoplakic vulvitis is a chronic inflammatory condition of unknown origin characterized in the early stages by marked hyperemia and cellular activity, and in its later phases by marked epithelial hypertrophy, and a thickened, sclerosed, and retracted condition of the subepithelial tissue. The whole of the vulva may be implicated with the exception of the vestibule and orifice of the urethra, which are never affected. It may extend laterally to the folds of the thigh and posteriorly to the external perineum and the skin around the anus. There are four clinical stages:

First stage: reddening, swelling, excoriation, and dryness.

Second stage: retraction with thickening, decrease in size of the greater and lesser lips, and change of color from red to white.

Third stage: cracks and ulcers with discharge and bleeding; tendency to carcinomatous change.

Fourth stage: complete involution; vulval surface smooth, shiny and white; disappearance of labia minora and clitoris from contraction of the subepithelial tissues; cessation of pruritus.

The symptoms are intense pruritus in the second and third stages with pain with acute sensitiveness in the third stage from the exposure of nerve endings in the cracks and ulcers. There are no symptoms in the fourth stage.

Kraurosis vulvæ consists of an atrophic condition of the vulva associated clinically with stenosis of the vaginal orifice and pathologically with certain changes in the dermis. It may involve all the surface of the vulva as far as the skin borders of the labia majora, and the skin of the perineum and anal region. Kraurosis vulvæ is divided into two stages:

First stage: the mucocutaneous surface, red and glistening, is dotted over with small patches varying in color from bright red to purple. The urethral orifice is in a caruncular condition.

Second stage: The mucocutaneous surface becomes yellow like that of a fatty liver. The surface ridges are obliterated. The vaginal orifice is greatly contracted; the labia minora and clitoris disappear; the mons veneris atrophies; the pubic hair breaks off or falls out. The condition is one simply of retraction and thinning. Pruritus is one of the rarest symptoms, the chief complaint being that of dyspareunia. In the first stage, the parts are sensitive, especially to the passage of urine.

Kraurosis. A comprehensive review of this subject by Savill[260] has served as the chief basis for this discussion. Breisky[38] was the first to call attention to the condition of contracted vaginal orifice; not all of his cases were associated with deficient ovarian function. Jayle[134] limited the term kraurosis to the atrophic contraction due to several causes and described a red and white variety as well as kraurosis combined with vulvitis and also with cancer. The red type is accompanied by a reddened urethra, or a caruncle, and with redness of the ducts near the urethra and the vaginal orifice. The lesion of leukoplakia chiefly involves the epidermis, while kraurosis affects the cutis as well and this leads to progressive atrophy and sclerosis. Graves and Smith believe that the clinical and histologic evidence indicate that kraurosis and leukoplakia used in the classic sense are phases of an identical process. Taussig[295a,b] reserves leukoplakic vulvitis for a state with pruritus, pain on urination, with white areas and subsequent contraction and sclerosis. Kraurosis he defined as the later stage, when the leukoplakic vulvitis has led to obliteration of the labial and preputial folds; thus the condition was seen with deficient ovarian function, in old women or those whose ovaries had been removed. In more than half the cases of leukoplakia vulvitis carcinoma supervenes (39 of 64 cases). He advised vulvectomy as the effective treatment. Montgomery and his associates[194] advocate limiting the term kraurosis to the condition described by Darier (progressive sclerosing atrophy of the mucocutaneous

teguments of the vulva, leading gradually to stenosis of the vaginal orifice, to the disappearance of the labia minora, the hood and the clitoris, and the effacement of the labia majora). The mucosa of the parts involved is smooth, shiny, dry; the color is white, waxy yellow, red or spotted. It may be complicated by leukoplakia and the chief pathologic condition in kraurosis is suppression of the ovarian function by senile involution, by sclerosing atrophy of castration; syphilis plays a rôle in certain cases. Montgomery, Counsellor and Craig conclude: (1) kraurosis is an atrophic process which may possibly lead to a malignant change; (2) leukoplakia of the vulva is a hypertrophic process, definitely a precancerous dermatosis, which frequently results in a malignant state; (3) pruritus vulvæ with lichenification (neurodermatitis) is a benign form of inflammatory dermatosis which does not *per se* result in a malignant change. Adair and Davis[4] regarded leukoplakia and kraurosis vulvæ as stages of the same disease. Ketron and Ellis[141] in an excellent review apparently look on leukoplakia and kraurosis vulvæ as the same process but point out that kraurosis vulvæ (leukoplakia) shows in a considerable percentage of cases peculiar degenerative changes in the connective tissue identical in appearance with those characteristic of their cases of white spot disease. They believe that some cases, at least, which are diagnosed leukoplakia are examples of white spot scleroderma of the vulva. Leukoplakia of the vulva (histologically acanthosis and hyperkeratosis) is probably frequently superimposed on various pathologic processes of the vulva whether primarily of a degenerative or inflammatory nature.

Savill does not believe that kraurosis has symptoms of itself. Any symptoms are due to superimposed infection which occurs from time to time. It occurs in elderly women and in younger women from whom the ovaries have been removed; in both cases preëxisting atrophy prevents the development of the hypertrophic stage with the keratinization seen with leukoplakic vulvitis. Savill believes that estrin preparations[242] aid by rendering the part more vascular and hence softening the sclerosis and diminishing the contraction. The relief obtained is usually only temporary. Relapse of symptoms occurs when local foci of infection become active. In the late phases, Taussig recommends vulvectomy. Savill has had good results from diathermy.

Tar Cancer—Precancerosis. The carcinogenic properties of tar have been mentioned elsewhere. The specific problem of tar cancer of the lip in fishermen was fully discussed by Shambaugh.[265] He found that fishermen in the Massachusetts region are exposed, in the handling and repairing of tarred nets, to the most strongly carcinogenic type of tar, namely horizontal retort gasworks tar. The lips are especially contaminated with the tar because of the frequent practice of holding the tar-smeared needle in the mouth while repairing the nets. On the basis of 8 cases, the author proposes the belief that exposure to tar may be partially responsible for the apparent high incidence of cancer of the lip in fishermen.

Verruca Senilis (Seborrheic Keratosis) and Keratoma Senilis (Senile Keratosis). Freudenthal[92] distinguished verruca senilis from keratosis senilis. His designation apparently referred to keratosis seborrheica and keratosis senilis respectively. Eller and Ryan[84] and Montgomery[193d] agree with Freudenthal that these are two distinctly clinical conditions, entirely different in their histologic structure and different in their predisposition to malignant change. Other authors (MacCleod;[180] Williams;[335] Pusey;[240] Lain[147]) use these terms synonymously. Still others (Unna and Delbanco quoted by Freudenthal) think that the difference, if any, is unimportant and merely an academic question. Sutton and Sutton[286b] believe that keratoses are intra-epidermal carcinomas of comparatively slow growth rate.

Montgomery (1935) has summarized the pertinent facts relating to these two types of lesion, which we believe are distinctive from the clinical and histopatho-

logic standpoints. Verruca senilis (seborrheic keratosis) usually develops in the later decades of life as multiple lesions of various size and occur chiefly in the trunk in the seborrheic regions although the face may be extensively affected. They begin as light yellow spots which increase in size, and become pigmented spots which increase in size, and become pigmented, some even bluish brown. A thin greasy scale, readily removed by friction, usually covers the lesions. They have the appearance of being stuck on the skin. Clinically they resemble and may be confused with pigmented nevi (Miescher; Häberlein and Guggenheim: *Arch. f. Dermat. u. Syph.*, **174**, 105, 1936), histologically with pigmented basal cell epithelioma.

Histologically these lesions show a characteristic picture, but one resembling dermatosis papulosa nigra (Michael and Seale[186]). The features are: nevoid grouping of the epithelial cells; islands of connective tissue which separate the groups; horn cyst formation; thickened horny layer; pigment granules in the basal cells; basophilic degeneration of the connective tissue fibers; mitotic figures rare; slight non-specific inflammation reaction in the cutis; slight edema of upper cutis. Occasionally they may appear in the form of a dry keratotic type which require histologic study for diagnosis. This type of lesion does not show malignant change unless it is subject to irritation and repeated trauma. When they do develop into malignancy the lesion is usually basal cell in type (Pinkus[231]). Excision, for cosmetic reasons, or if the lesion is in site of irritation, usually gives a good result. Radiotherapy is not a treatment of choice because of the marked degree of differentiation of the individual cells.

Senile keratoses (*keratoma senilis*) also occurs chiefly in older individuals, but on the backs of the hands and on the face. They may appear anywhere on the body. People exposed to the elements, sun, wind, extremes of weather, are especially prone to develop them. They are accordingly frequent among sailors, farmers, and those who have so-called sailor's skin. Senile keratoses are discrete, appear as verrucous, brown to grayish keratotic papules, or as ill-defined sealing patches. The scales are dry and adherent and their removal may result in points of bleeding. Evidence of a peripheral zone of erythema together with a sense of palpable induration is, as a rule, indicative of malignancy. Occasionally a senile keratosis develops into a cutaneous horn. The subject of cutaneous horn has been admirably reviewed by Douglas Montgomery.[192] The histologic features are marked hyperkeratosis with or without a tendency to verrucous formation; acanthosis; parakeratosis (variable feature); inflammatory reaction of variable degree in the upper cutis; basophilic degeneration of upper cutis; pigment granules in the basal cell layer not a distinguishing feature; mitotic figures more frequent than in seborrheic keratosis; no interlacing of epithelial cells, no horn cysts; but edema of epidermis (basal cell layer). Montgomery believes the histologic features of senile keratoses are less distinctive than in seborrheic keratoses. He believes that senile keratoses develop into squamous cell epitheliomas in 20 to 25% of the cases. Of these, 90% are squamous cell in type with individual cell keratoses similar to the picture of early Roentgen and radium epitheliomas (Hookey,[123] Montgomery and Dörffel,[195] Montgomery[193g]). This viewpoint is criticized by Sutton, Jr.,[287b] however.

Treatment of senile keratoses by irradiation with Roentgen rays is illogical, according to Montgomery.[193f] A good cosmetic result without recurrence may be obtained by thorough fulguration or by light use of the cautery or diathermy.

Xeroderma Pigmentosum. The literature on this subject has been reviewed recently by Beerman and Stokes[27] and by Macklin.[173] Macklin reported a case and presented a consideration of incomplete sex linkage in inheritance of the disease. Loewenthal and Trowell[168] reported 3 cases in an African Negro family, a race presumed to be immune to xeroderma pigmentosum.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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CIGARETTE SMOKE, IRRITATION AND THE THROAT

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Since an impressive number of people smoke cigarettes, the effect of cigarette smoke on the human throat is a subject of widespread interest. Despite this, however, most currently published nose and throat text-books either completely ignore the problem or touch upon the theme superficially. It is not surprising, therefore, that among many physicians much unsubstantiated opinion prevails as pseudoscientific belief.

The purpose of this review is to survey the pitfalls of disputed territory and to attempt to arrive at sane conclusions.

Cigarettes and Cigarette Smoking. According to Proetz,[10] the typical American cigarette consists chiefly of American tobacco, with an admixture of Turkish, Egyptian, Greek and other components, cured according to various processes. It is flavored with mixtures of volatile substances which impart to the individual brands their characteristic tastes and aromas. In occasional instances a distinct flavor is imparted by one or another of these ingredients: this occurs with cigarettes containing menthol. The combustion products of burning tobacco leaves which constitute smoke depend not only upon the character of the burning material, but also upon the position of the cigarette while burning; the speed of the puff; the volume of the puff; the frequency of the puffs; the number of puffs in the series; and the humidity of the tobacco and of the room.

The number of puffs taken in smoking a cigarette is highly variable, depending on both the cigarette smoked and the smoker. Tightly packed cigarettes burn more slowly than those loosely packed and therefore afford more puffs. The main variable, however, is the smoker. While reading, writing, playing cards or similarly occupied, he may take only 3 or 4 puffs from the entire cigarette; again, in moments of nervousness he may smoke with great rapidity. Haggard and Greenberg[6] observed that a large number of subjects who were habitual smokers, smoking the particular cigarettes under study and with their attention fixed on smoking, showed an average of 17 puffs per cigarette, with extremes of 13 and 22.

The mouth, not the chest, is used to draw in the smoke from a cigarette, and the act is identical with sucking. In taking a puff the pharynx is shut off, the lips are closed about the cigarette and the cavity of the mouth is enlarged by the movement of the tongue. The amount of air that can be drawn into the mouth under these circumstances is limited. Measurements of the volume of air drawn in with a single puff from a cigarette gave an average value of 33 cc., with extremes of 22 cc. and 51 cc. After cigarette smoke is drawn into the mouth, the passage to the larynx is then opened and an inspiration made. The amount of air drawn in corresponds closely with that of a normal inspiration, or about 500 cc. The inhaled air is thus diluted with more than 15 times its volume of fresh air. This diluted air is still further diluted with the stationary air in the respiratory passages, and the

final mixture is exhaled. An occasional smoker, after taking the smoke into the mouth, draws it into the pharynx and exhales it through the nose; the dilution under these circumstances is only to the extent of the volume of air contained in the pharynx and in the nasal passages.

Ballenger and Johnson[1] assert that the products of the combustion of tobacco include carbon dioxide, carbon monoxide, nicotine, ammonia and aldehydes, such as acrolein, formaldehyde, furfural, tars and formic acid. It has not been definitely established which of these various products of combustion is the major factor in a possible irritation of the mucous membrane. Suspected as principle irritants are acrolein, formaldehyde, formic acid and possibly furfural. These products are present in smouldering and burning vegetation. The speed and manner of smoking enter into the rate of production of these possible irritants. In the opinion of Bogen,[2] fast smoking increases the carbon monoxide and nicotine content of the smoke and to a lesser extent the aldehyde content. "Heat, free nicotine, pyridin and other nitrogenous bases, volatile acids, tarry and phenolic substances and particularly the aldehydes liberated in the smoke, of which furfural and acrolein have been especially condemned, may all contribute to the irritation of the mucous membranes of the smoker." Bogen believes that nicotine plays a small part in local irritation. If the last third of the cigarette is smoked, the nicotine and probably the other constituents of the smoke are greatly increased, which may or may not have an increased irritating effect on the mucosa. Ammonia is given off in the "side stream" but seems to be absent in the "main stream" of the smoke. Cigarette paper gives no harmful products unless nitrate has been added.

Animal Experimentation. In order to insure a satisfactory moisture content some hygroscopic agent is customarily added to cigarette tobaccos. For this purpose glycerin has long been used. In several publications[9a,9b,11] it has been indicated that smoke from cigarettes containing diethylene glycol is less irritating than smoke of cigarettes made with glycerin or even devoid of any added hygroscopic agent. Such, for instance, were the observations of Mulinos and Osborne who prepared solutions by drawing smoke from the various types of cigarettes through a small volume of physiologic salt solution, water, oil or Ringer's solution, and then noted the resulting irritation when these smoke solutions were instilled into the conjunctival sac of rabbits. They chose as a criterion of irritation the edema-provoking properties of the smoke solution and found the solutions made from diethylene glycol-impregnated cigarettes to be least irritating.

This pronouncement prompted Haag[5] to repeat the animal experimentation, employing as far as possible the general technic described. All cigarettes were selected of a uniform weight, standard in physical properties, and of the same normal moisture content. Five-sixths of each cigarette was smoked in a conditioned laboratory atmosphere at 85° F. and 45% relative humidity. The average cigarette was consumed in 8 minutes. The smoke was drawn through 3 cc. of physiologic salt solution, and the smoke solutions of the 2 types of cigarettes were prepared simultaneously and employed experimentally the same day.

In performing the animal observations, Haag used 3 drops of the smoke solution, instilling them into the left eye of the rabbit, the right eye serving as a control. As evidence of the degree of irritation provoked, the objection of the animal and the blepharospasm, as well as the extent and duration of the hyperemia and edema of the conjunctiva were tabulated at regular intervals of several minutes. It appears from Haag's results that there was no significant difference, either as to intensity or duration, in the irritation produced by the instillation into the rabbit eye of the 2 smoke solutions studied. He concludes that when aqueous smoke

solutions, obtained from diethylene glycol-treated and glycerin-treated cigarettes, were instilled into the conjunctival sac of rabbits, no differences in the irritating properties of the 2 types of cigarettes were observed, as judged by the appearance of hyperemia, edema, blepharospasm and the objection of the animal.

McNally[8] and his associates, using hyperemia as the criterion of irritation, also studied the irritating properties of smoke from tobacco treated with glycerin and diethylene glycol. Finding no significant difference between the smoke from the 2 types of tobacco or between either of these and the smoke from plain tobacco, they declare: "Our own work is in complete harmony with the view that no significant difference exists. Many of the authors cite the difficulty in interpreting the observations, both clinical and laboratory, yet Mulinos and Osborne were able to note 8 different degrees of edema! If differences in effects are so slight as to be difficult to classify by the majority of observers, how can such differences have *any* practical significance?"

Weatherby,[12] using the trypan blue technique involving intradermal injections in rabbits' ear, also found no difference between the 2 types of cigarette smoke.

Clinical and Laboratory Investigations. Flinn[4] enumerates a number of difficulties associated with a strictly clinical study of the effect of cigarettes. He states that in a study of the effect of smoking on the mucous membrane of the nose and throat there is no scale by which one can express the degree of congestion; that one must depend on personal impressions which cannot be carried with exactitude to another examination 1 week later; and that one cannot take tissue and compare it in a colorimeter with a known standard so that it can be expressed in terms that will correspond to the determinations made by another observer. Having established these premises, Flinn veers away from their soundness and concludes from clinical observations that the smoking of diethylene glycol-treated cigarettes seldom causes irritation, and that indeed it actually appears to be followed by an ameliorating effect upon an irritated throat and tongue.

In an effort to determine by clinical means the presence of any irritating properties of the hygroscopic agent used in cigarettes, Ballenger and Johnson observed 100 subjects. The cigarettes were identical in composition except in the hygroscopic agent used. One lot contained glycerin, a second diethylene glycol, and a third had no hygroscopic agent. They conclude that the hygroscopic agent used in cigarettes is not a factor of importance in producing symptoms or in producing objective evidence of irritation of the nasal or throat mucosa.

In a study of cigarette smoke and its effect upon the respiratory tract conducted by Proetz, 26 subjects were observed by 8 trained physicians. The observers were instructed to examine the throats of the subjects and to classify their findings according to the following: (*a*) throats having no suspicion of any inflammatory reaction, so-called normal throats; (*b*) throats showing minor signs of irritation or inflammation of no clinical importance; (*c*) throats definitely red and inflamed; and (*d*) severe sore throats, of the type usually associated with fever and other systemic symptoms. After an inquiry into the reliability of simple comparative clinical observations of the pharyngeal mucous membrane he came to the conclusion that "Regarding the reliability of simple clinical observation as a basis for statistical studies of the pharynx, even under the best conditions and with the problem clearly defined in the mind of the examiner, we find a diversity of opinion (*i. e.*, among 8 trained medical observers) reaching 79%." Just what are the objective changes produced in the mucosæ by the protracted action of cigarette smoke was not determined. Belief is expressed that it is not at all certain that they may be classified in terms of color, or even that progressive irritation results in progressively heightened color.

Holck and Carlson[7] maintain that the method employed by Mulinos and Osborne is not quantitative and that the method used by Flinn is also not quantitative. It is known that within physiologic limits irritation of the mucous membranes of the mouth give rise to increased salivation. Tobacco smoke is an irritant known to stimulate salivary flow. If glycerin added to tobacco increases the irritating properties of the smoke, one would expect a greater flow of saliva from the smoking of tobacco treated with this hygroscopic agent, and if diethylene glycol markedly decreases the irritative properties, the reverse would be expected. With these considerations in mind, experiments were undertaken to measure the salivary responses of 26 men and 2 women. This method of measuring the degree of irritation caused by smoke was employed because the buccal cavity is normally the place of entrance of tobacco smoke, and because it gives an objective quantitative measurement.

The average responses of the 28 subjects to the 3 kinds of cigarettes—glycerin-treated, diethylene glycol-treated and hygroscopic agent-free—agreed very closely, so that there was not the slightest indication that one cigarette was more irritating than another. The data of Holck and Carlson give no indication that cigarettes can be classified consistently as to the irritating quality of the smoke by supposedly normal human beings. In many instances the same kind of cigarette was at one time called mild and at a subsequent period pronounced irritating by the same person. It is believed that a method for determining the irritating properties of cigarettes which relies solely upon the opinions of ordinary smokers cannot be called reliable.

In order to eliminate some of the disadvantages inherent in methods employed elsewhere—namely, (*a*) efforts to acquire data from mechanical or robot smokers consisting of glass tubes and flasks which, at best, provide neither the human subject nor the precise conditions under which human beings smoke; (*b*) the unsatisfactory conclusions that can be drawn from experiments on rabbits' eyes, an anatomic site which is not comparable to the human throat; and (*c*) the lack of reliable information that can be obtained from clinical observation of the human throat—Fabricant[3] measured the effect of cigarette smoke on the normal, physiologic range of the pH of the mucous membrane of the human throat. A silver-silver chloride glass electrode in conjunction with an electrometer was employed. In essence, studies of the pH of the mucous membrane of the throat apply a laboratory procedure in a clinical environ. The subjects were 100 men and women with clinically normal throats.

Three kinds of cigarettes were used in the experiments: cigarettes containing glycerin, diethylene glycol, and those without a hygroscopic agent. In the conduct of the experiments the speed and volume of the puff, the frequency and number of puffs and the position of the cigarette while burning were left entirely to each smoker's preference and habits. Some of the smokers discarded a cigarette after a half-dozen puffs; the majority, however, discarded it much later. While some inhaled deeply, others did not. Each smoker was cognizant of the type of cigarette he was smoking. No attempt was made to alter in any way a smoking technique which may be called the average smoking habit.

The effect of smoking 2, and even 3, dissimilar cigarettes within a prescribed period indicated no abnormal alteration of the normal, physiologic pH of the throat. The smoking of a glycerin-treated cigarette did not disturb the normal, physiologic pH range of the mucous membrane of the throat. A comparison of the effect of the glycerin-treated cigarette and that of the diethylene glycol-treated cigarette failed to show any difference between them. Further, there was no difference between the diethylene glycol-treated cigarette and the cigarette devoid of a hygroscopic agent, nor was there any difference between the effect of the gly-

cerin-treated cigarette and that of the hygroscopic agent-free cigarette. Although in this series of 100 subjects there was no incompatibility between the smoking of cigarettes and the normal, physiologic pH values for the throat, it is conceivable that a tobacco-sensitive or tobacco-allergic person or one with an acutely inflamed throat might show alterations in the pH range.

The question as to the possible harmful effects of smoking cigarettes containing menthol has been investigated by Haggard and Greenberg. The amount of menthol in mentholated cigarettes on the American market was found to range between 1 and 2 mg. per cigarette. Approximately one-half the menthol in the cigarette is lost by combustion; the other half appears in the smoke. On inhalation of the smoke approximately 70% of the menthol is absorbed, an amount so small as to be innocuous. Five minutes after a subject has smoked a mentholated cigarette, menthol cannot be found in the saliva or in the expired air.

Comment. At one time or another various components of cigarettes, cigarette smoke and tobacco combustion—heat, nicotine, pyridine and pyridine derivatives, carbon dioxide, carbon monoxide, ammonia, the aldehydes, acrolein, formaldehyde, formic acid, furfural, tarry and phenolic substances, and cigarette paper—have been declared responsible for throat irritation. All investigators in the field of tobacco research are agreed that it has not been definitely established which of these various components is the major factor.

Methods for determining the irritating properties of cigarettes which rely solely upon the opinions of ordinary smokers cannot be called reliable. Clinical studies of the effect of cigarette smoke on the human throat for comparative purposes are also unreliable. Unsatisfactory conclusions are drawn from experiments on rabbits' eyes, an anatomic site which is not comparable to the human throat.

In order to insure an adequate moisture content some hygroscopic agent—glycerin or diethylene glycol—is customarily added to cigarette tobaccos.[1] Preponderant investigative opinion indicates that there are no differences in the irritating properties of the 2 types of cigarettes.

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PHYSIOLOGY

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SESSION OF FEBRUARY 19, 1946

Di-isopropyl Fluorophosphate, a New Irreversible Anticholinesterase Agent. GEORGE B. KOELLE, PH.D., 1st LT., M.A.C., and ALFRED GILMAN, PH.D., MAJOR, SN.C. (Med. Res. Lab., Chem. Warfare Service, Edgewood Arsenal, Md.). The alkyl fluorophosphates, first synthesized by Lange and von Krueger and later studied by British and American investigators as potential chemical warfare agents, have been shown to act as irreversible anticholinesterase agents. Certain aspects of the pharmacology of di-isopropyl fluorophosphate (DFP) have been investigated to provide a background for its clinical trial in the treatment of myasthenia gravis and glaucoma.

When rats were given intramuscular injections of DFP, the relative degrees of inhibition of the cholinesterases of brain, muscle, red blood cells and serum were found to correspond fairly closely to their *in vitro* sensitivities. The regeneration of serum and red cell cholinesterase required about 2 weeks in this species, while about 100 days were necessary for the restoration of brain and muscle cholinesterase. Symptomatology and serum and red cell cholinesterase activity were followed in dogs and monkeys following the administration of single doses of DFP. It was concluded that measurements of the degree of inhibition of serum or red cell cholinesterase do not provide a reliable indication of the activity of the enzyme in the tissues.

Chronic toxicity studies were conducted on dogs receiving repeated high doses, and dogs, monkeys and rats receiving repeated moderate doses of DFP over periods of from 3 to 6 months. Both dogs on the high doses developed cardiospasm, urinary incontinence and paralysis of the hind legs. Bronchopneumonia occurred in 3 of the 4 monkeys, terminating fatally in 1. In neither of these species did abnormalities appear in routinely performed red cell counts, white cell counts, differential counts, or blood sugar, plasma NPN, serum protein, or hepatic function determinations. The rats developed no effects attributable to the drug.

The Influence of Di-isopropyl Fluorophosphate on the Normal and Glaucomatous Eye. IRVING H. LEOPOLD, M.D., D.Sc. (Department of Ophthalmology, Hosp. Univ. of Penna.). The length, speed and intensity of action with di-isopropyl fluorophosphate was determined on the eyes of the rabbit, cat, dog and man. Di-isopropyl fluorophosphate was found to be more prolonged in its action than any other known miotic agent in the concentrations used. Studies on the denervated iris of the cat's eye disclosed that this agent worked solely by its anticholinesterase activity. In the concentrations used on the normal eye this agent produced considerable ciliary spasm, false myopia and subjective symptoms related to the ciliary spasm. The rate of diffusion of fluorescein and inulin from the blood stream into the anterior chamber of the normal rabbit eye and into the rabbit eye under the influence of DFP was determined. The results of the trial of di-isopropyl fluorophosphate in glaucomatous eyes showed that this agent has definite potentialities in the medical treatment of glaucoma.

A Study of Carbon Dioxide Assimilation in the Rat With Isotopic Carbon. ADELAIDE M. DELLUVA, M.S., and D. WRIGHT

WILSON, PH.D. (Dept. of Physiol. Chem., Univ. of Penna.). The utilization of carbon dioxide by animal tissues *in vivo* was studied. An adult female rat was injected intraperitoneally with isotopic sodium bicarbonate solution. The injections of the isotonic solution were made at 1 hour intervals for a period of 18 hours with 5 ml. of solution each time. The rat was killed by severing the carotid artery ½ hour after the last injection. Analyses were made of the pooled urine, pooled feces, long bones of the fore and hind legs, and fat-free proteins of the liver, muscle, and kidney (the kidney fraction included the spleen and part of the small intestine). Isotope was found in the carbonate of the urine, carbon of the urea, carbonate of the bone, alpha-carboxyl carbon of the glutamic acid, the carboxyl carbons of aspartic acid, and amidine carbon of arginine. There was very little isotope in the carbonate of the feces. The position of the labelled carbon in the arginine coincided with what would be expected from an operation *in vivo* of the ornithine cycle for urea formation. The isotope location in the glutamic and aspartic acids was in accord with the positions of tagged carbon to be expected in the products of transamination of isotopic oxalo-acetic and alpha-ketoglutaric acids formed during the assimilation of labelled carbon dioxide.

The Passage of Endogenous Estrogen Across the Parabiotic Union in Rats. ISOLDE T. ZECKWER, M.D. (Dept. of Pathol., Univ. of Penna.). When an ovariectomized rat, A, is united in parabiosis with a litter-mate female rat, B, the pituitary of A hypersecretes FSH which passes to Rat B, causing secretion of estrogen by the ovaries. In the early stages, the vagina and mammary glands of A are atrophic; the vaginal epithelium of B, cornified. In less than 1 month, estrogen in B releases LH from the pituitary of B, with development of many large corpora lutea. At this stage, estrogen passes from B to A, resulting in cornification of vaginal epithelium in A, and coincident with this, the vaginal epithelium of B changes from cornification to mucification. It is known (Biddulph *et al.*) that when exogenous estrogen is injected into 1 of a pair of rats, 40 times the dose that is effective in the single rat is required to permit passage of estrogen across the parabiotic union. Consequently the level of endogenous estrogen in B must be very high at the time that it passes to A. Therefore, progestin from the corpora lutea has not resulted in lowering the blood level of estrogen. Mucification of vaginal epithelium is known not to be a positive effect of progestin, as progestin alone causes no histologic change in vaginal epithelium, but is due to the effect of estrogen antagonized by progestin (according to Korenchesky and Hall, in the proportion of 1500 γ progesterone to 1 γ estrone). It is concluded that in the parabiotic rats, this modification of the effect of estrogen by progestin must take place in the reacting tissues, not in the blood stream. After a month or longer, these changes are replaced by the well-known atrophic changes in A and the effects of constant estrogen without progestin in B which last many months.

BOOK REVIEWS AND NOTICES

MEN WITHOUT GUNS. Text by DEWITT MACKENZIE, War Analyst of The Associated Press. Descriptive Captions by MAJOR CLARENCE WORDEN, Medical Department of the United States Army. Foreword by MAJOR GENERAL NORMAN T. KIRK, Surgeon General of the United States Army. Pp. 152; 137 ills. Phila.: Blakiston, 1945. Price, $5.00.

THIS book records in words and pictures the services of our doctors, nurses, and enlisted men on the battlefields and in the hospitals of Europe and Asia. A dozen American artists contributed to the notable series of paintings. These artists are: John Stewart Curry, Fred Shane, Manuel Tolegian, Ernest Fiene, Franklin Boggs, Robert Benney, Joseph Hirsch, Lawrence Beall Smith, Howard Baer, Francis Criss, Peter Blume, and Marion Greenwood.

The book is filled with the exciting drama of modern warfare and is a valuable record of the men who fought without guns for the second World War. D. C.

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